INTRODUCTION

The application of polymers as medical devices has steadily increased in almost all medical fields because of the versatility of these materials. Thus, research has focused both on the development of more appropriate materials for specific situations and on the modification of already useful materials for the improvement of their intrinsic properties. Modifications on this kind of materials have increased their potential uses by adapting their mechanical properties to specific needs. Moreover, biocompatibility of the polymeric materials has been improved by the inclusion of certain functional groups, providing responses to physical and chemical stimuli present in physiological conditions.

Until recently, one of the most worrying problems in hospitals has been infections derived from medical devices usage. Typically, this kind of infections was handled with the use of prophylactic and therapeutic treatments with ‘classic’ (low-molecular weight) antimicrobial agents. This strategy has been effective in most patients suffering from nosocomial infections. However, it has the disadvantage of substantially increasing the probability of antimicrobial-resistant pathogens appearance, which continue to be especially dangerous in hospital environments (Cohen et al., 2017; World Health Organization, n.d.; Zegers et al., 2017). Additionally, due to...
the hydrophobic nature and roughness of biocompatible polymers for medical devices (De-la-Pinta et al., 2019), microbe adhesion and biofilm formation is probable on this type of materials, increasing the risk of infection development on the vicinity of these devices (e.g. tissues near wound dressings, urinary catheters, implants, etc.). While treatments with ‘classic’ antimicrobials could be administered orally or intravenously, a localized effect on the infections is not always attained. Taking these issues into account, one of the most promising strategies is the production of polymeric devices which exhibit antimicrobial properties.

The production of polymers that are able to prevent the growth of pathogens of different species such as bacteria, fungi, algae and yeasts is a huge area of research. This is due to the great variety of techniques used to prevent pathogen growth as well as to the great variety of targeted pathogenic microorganisms (Narayana & Pichika, 2019). Recently, the focus of the research has been the development of antibacterial polymers (polymers which only prevent the growth of bacteria), which have been proven to be biocompatible, effective and able to resolve the issues related to the use of ‘classic’ antibiotics (Arora & Mishra, 2018). Many other antimicrobial polymers have already proven to be just as useful for combating other kinds of infections produced by both bacteria and other pathogens. Since antimicrobial systems are less considered as focus for the research community, with this mini-review we seek to make a brief compilation of advances in antifungal polymeric medical devices by presenting the most common examples of polymeric antifungals, a brief explanation of general mechanism of action, and their most important classifications.

This review focuses on fungi-associated infections, since the worldwide occurrence of fungal infections has been steadily increasing. Fungal infections caused by drug-resistant organisms are an emerging threat to heavily immunosuppressed patients with haematological malignancies. We chose this topic because the spotlight for reviews about antimicrobial substrates are mainly antibacterial materials and fungal infections are very common in humans, since fungi can grow in wet and dry areas. Additionally, these infections are also associated with drug-resistant fungi and yeasts, and skin infections are the most common fungal diseases in humans (De Pauw, 2011). Some estimates indicate that the rate of fungal disease has surpassed at least one billion infections worldwide, with many strains of fungi causing hospital-related infections and high mortality rates on patients with compromised immune systems such as those with cancer, HIV-positive diagnoses (Bongomin et al., 2017; Fisher et al., 2012) or haematological malignancies (Gamaletou et al., 2018). Generally, for human infections, the most common fungi and yeasts are Candida, Aspergillus, Trichophyton rubrum, Blastomyces, Saccharomyces, Histoplasma and Cryptococcus spp. Thus, the main purpose for this research field is to inhibit their growth and mitigate the diseases. As mentioned before, current treatments for this kind of infections include the administration of organic fungicides such as polyenes, azoles or lipopeptides. Furthermore, some of these compounds are introduced in topic formulations to deal with fungal keratitis or skin infections (Garber, 2001; Pfaller et al., 2006).

Unfortunately, just as other pathogens, the increased use of ‘classic’ antifungals has led to the development of antifungal resistant strains which are even more concerning (Wiederhold, 2017).

Although antifungal polymers have the common characteristic of stopping the propagation of different kinds of fungi, these materials differ substantially on the strategy they use for inhibiting their growth. The difference on their mechanism of action allows the following classification which will be important throughout this review:

- Inclusion of intrinsically antifungal moieties on a polymeric structure. (e.g. quaternized ammonium salts, azole groups).
- Modified polypeptide macrocyles and echinocandins.
- Polymer composites containing metallic or organic antifungal agents.
- Polymer architectures for the release of low-molecular weight antifungals (e.g. inclusion of Amphotericin B on polymeric micelles).

It is important to note, that although all the classifications have their own advantages and disadvantages, each of this kind of antifungal polymers have their own challenges in the design, synthesis, production and applicability. It is important to mention that one of the most challenging steps in finding antifungal agents is coming from the fact that both fungi and mammal cells are eukaryotes, which tend to complicate the finding of non-cytotoxic fungicidal compounds. This is in clear contrast to the situation with antibacterial compounds in which the differentiation between prokaryotic (pathogen) and eukaryotic (mammal) cells allows for easier selectivity (Liu et al., 2013). Although the main difference between prokaryotic and eukaryotic cells is the presence of a nucleus, another important difference is the presence of peptidoglycan in the cell wall. Nevertheless, both antibacterial and antifungal drugs affect cell wall or membrane in similar way, by disruption processes of the cell membranes/walls. It is important, however, to mention that these disruption processes depend greatly on the mechanism of action of each antimicrobial drug, specifically the target enzymes which are activated or deactivated on these processes (e.g. hydrolysis of glycans or electrostatic interactions). At the current stage of development of these materials, the research has focused in finding the appropriate chemical substrates that can be both antifungal and biocompatible. Although this may be an objective numerical indicator of the usefulness of the material in a general scenario, it is not trivial to say which material or type of material will be the best option since each material may be better suited for a specific application. As the research advances, the clinical demands for specific antifungals will help for the discrimination of certain substrates for many uses.

Additional to this classification, it is possible to differentiate between antifungal macromolecular materials by considering their possible applications; for instance, some materials may be better suited for medical devices, while others may be better suited for water purification. These differences in applications are crucial when evaluating the properties of a material and are therefore discussed briefly in each of the sections of this work. As a final point to mention, most of these materials are in an early stage of
development; thus, the applicability of these in a clinical context may be limited to the testing and effectiveness of these materials as medical devices or as drug formulations. Therefore, this review focuses on the production of materials which showed promising antifungal properties and may be later exploited as tangible medical applications.

As a guide to the reader and as a final note to the introduction, we add a brief table of contents to summarize the content of the review. As such, the present review is divided in the following sections:

1. Polymers with antifungal moieties
   (a) Cationic antifungal polymers
   (b) Azoles
2. Fungicide addition to polymers
   (a) Metal-loaded polymers and composites
   (b) Addition of organic-fungicide compounds to polymers
3. Drug delivery systems
4. Polyelectrolytes and echinocandins
5. Other antifungal polymers

## 2 | POLYMERS WITH ANTIFUNGAL MOIETIES

Low-molecular weight antifungal molecules and the specific moieties which allow for their antifungal activity are well documented and readily used on the medical industry. For instance, topical and oral formulations of clotrimazole, fluconazole and ketoconazole have been commonly used for the treatment of many fungal infections for decades and even have been available as over the counter medications in some of their pharmaceutical forms (Choi et al., 2019; Patton et al., 2001; Sawyer et al., 1975). In contrast, their polymeric counterparts have been only recently researched in a thorough manner and have often been related to the corresponding research on antibacterial polymers. It is important to note that although the inhibition effect of antifungal polymers is the same as the one of low-molecular ‘classic’ antifungals, their mechanisms of action are usually focused on the vicinity of the cell membranes, since polymer molecules are not prone in migrating within the insides of pathogen cells. In any case, the majority of polymers that have been proven to be antifungal must have cationic moieties so that the polymers have an overall positive charge density which are antifungal via the disruption of fungal cell membranes (e.g. quaternary ammonium and phosphonium salts), or contain moieties which are ‘classically antifungal’ through inhibition of crucial processes for fungi proliferation (e.g. azole rings), or that exhibit both properties (e.g. azolium rings) (Jiao et al., 2017; Long et al., 2017). With this in mind, in this section, for both cationic antifungal polymers and polymers with moieties which ‘classically’ inhibit fungi proliferation, their summarized mechanisms of action, important examples of each classification and recent advances on each field will be discussed.

### 2.1 | Cationic antifungal polymers

Cationic polymers and macromolecules are arguably one of the most extensively researched in antimicrobial polymeric materials as these substrates tend to be very effective antibacterials and antifungals. Even though the mechanism of action for this kind of polymers is not universally accorded, it is believed that the positive charge on these macromolecules inhibits the growth of pathogens by disrupting the cell walls and membranes of microorganisms (negative charge), promoting lysis of the contents of the cell. In this sense, both bacteria (especially gram-positive bacteria) and fungi are susceptible to this effect and are therefore often evaluated similarly when testing this kind of polymers. Even when all cationic polymers must bear a positive charged moiety, this characteristic is not enough to effectively disrupt the cell walls of pathogens such as fungi; for that purpose, functional groups that are effective in antifungal polymers must have certain characteristics.

Firstly, one of the most important characteristics of the charged functional groups is their identity since this determines both the synthetic availability of the materials and the potential for modification of a material. In general, the most common cationic moieties of antifungal polymers are quaternized ammonium and phosphonium salts from which ammonium salts are more prevalent. These types of salts are very common due to the existence of an enormous variety of techniques for their synthesis and the inclusion onto polymers (Arora & Mishra, 2018). Most of the salts contain pendant alkyl chains bounded to the heteroatom (nitrogen or phosphorus) (see Figure 1), which may be specifically selected during the synthetic protocol, so that the resulting material has specific behaviours or characteristics. It is important to note that although cell lysis is one of the most common mechanism of action for this kind of substrates, other mechanisms exist that may potentiate the effect of the positive charge and may be modulated by the identity of the alkyl groups attached to ammonium and phosphonium moieties, as well as by the backbone of the polymer. Some examples will be presented in this section (Jiao et al., 2017).

Secondly, one of the most important characteristics of this kind of polymers is the density of positive charge within the macromolecules, which directly affects the effectivity of the polymers in disrupting the cell walls of fungi. In general, more charge density implies a greater disruption capability. This parameter depends on the identity of the backbone of the polymeric material, the amount of charged groups within the polymer backbone, the identity of the charged functional groups, the presence of ramifications on the...
Another important characteristic that influences the behaviour of these polymers against fungi is their hydrophobic/hydrophilic balance. This parameter must be well balanced, since excessively hydrophobic surfaces (including polymer films and medical devices) are susceptible to protein adhesion which may promote fungi biofilm formation and excessively hydrophilic substrates may not only be toxic to pathogenic cells but also to host cells. The amphiphilic character may be easily modified by altering the identity of the pendant alkyl chains of ammonium or phosphonium salts. Even though it might not be universal for all polymers, chain sizes between 6 and 8 carbons have shown to be best effective in inhibiting pathogen growth (both bacteria and fungi) without being toxic to mammal cells (Ergene et al., 2018; Muñoz-Bonilla & Fernández-García, 2012; Xue et al., 2014).

A final parameter that is also important to control is the identity of the counterion (anion). This is due to mainly three facts: firstly, the dissociation of the polymer-counterion salt is a very important step in the interaction of the antifungal polymer and the pathogenic cells; therefore, the counterion must not be strongly bounded to the polymeric cation. Secondly, the identity of the counterion (especially the size and chemical characteristics) may affect the hydrophilic/hydrophobic balance of the polymer, especially when using large polymer substrates or the charged functional group, and on the average molecular weights of the material (Kenawy et al., 2007).

Another interesting system that has received a lot of attention recently is chitosan, specifically cationic derivatives of this substrate. Chitosan is one of the most abundant natural polysaccharides on the planet (second only to cellulose), and this linear polysaccharide is composed by random structural units of D-glucosamine and N-acetyl-D-glucosamine and is obtained through the partial deacetylation of chitin as shown on Figure 2 (Pérez-Calixto et al., 2016). Apart from being extremely abundant and being biocompatible, Shin and collaborators demonstrated that this polymer has intrinsic antimicrobial properties against gram-positive bacteria such as S. aureus and possess intrinsic antifungal properties by inhibition of crucial metabolic processes for fungi species such as C. albicans and S. cerevisiae (Shih et al., 2019). Additionally, chitosan has been used in combination with other antifungal compounds and has been used in the development of fungicide-delivery systems (as it will be discussed in following sections).

Although chitosan by itself presents crucial advantages as an antifungal substrate (at least for common pathogens for humans), its use is limited by its solubility in aqueous (and non-aqueous) media. To overcome this drawback, the most common modification for chitosan is the alkylation of its amino groups to form cationic N-substituted chitosan derivatives. This not only allows enhanced solubility of the polysaccharide, but also gives the possibility to freely integrate cationic saccharide, but also gives the possibility to freely integrate cationic ammonium or phosphonium moieties to the chitosan polysaccharide backbone.

A recent example of a modification of this nature was presented by Huang Jianying and collaborators, in which a modified antifungal chitosan that could be useful for oral medications was obtained. In this work, the modified chitosan was produced by treating chitosan with 4-chlorobutyryl chloride. The nucleophilic substitution of the obtained N-chlorobutryrylchitosan lead to the formation of the ammonium derivative of chitosan, N-(1-carboxybutyl-4-pyridinium) chitosan chloride (Figure 3). This modified chitosan derivative was effective in inhibiting the growth of two different fungi species with higher effectiveness than pure chitosan, as shown on Table 1 (Jia et al., 2016).

In another example of chitosan modification, quaternized N,N,N,N-tetramethylchitosan was produced by a two-step method involving the formation of a Schiff base intermediate on the amino group of chitosan, and its reduction followed by methylation with methyl iodide (Tabriz et al., 2019). These chitosan cationic derivatives along

![Figure 2: Partial deacetylation of chitin to produce chitosan](image-url)
with pristine chitosan were embedded within polyethersulphone membranes and tested for antifungal activity and hydrophilicity. In all cases, the inclusion of chitosan generated antifungal activities, which were visually detected in petri dishes zone of inhibition test \(^1\) with notable results from the membranes that contained quaternized N,N,N-trimethylchitosan, in which there was notorious inhibition of growth of Aspergillus niger. According to the results for this research, these membranes may be used for water purification and filtration processes (Tabriz et al., 2019).

A final series of examples of chitosan modification is the work presented by Wenqiang Tan and collaborators from 2017 to 2020. They presented the incorporation of different functional groups onto chitosan with an array of synthetic techniques as a mean to inhibit different species of fungi relevant to agriculture and to improve water solubility of the chitosan derivatives. In this work (Figure 4a), a combination of phosphonium and ammonium salts was introduced by chitosan amine groups alkylation and nucleophilic substitution to form the quaternary alkyl and allyl phosphonium groups (Tan et al., 2017). In another paper (Figure 4b), the research group modified chitosan nitrogen with two methyl groups and a different array of pyridinium groups through Schiff base intermediates to form quaternary ammonium antifungal polymers (Wei et al., 2018). In a follow-up study (Figure 4c), the same research group used azide—alkyne click reactions to include quaternary ammonium onto chitosan (Tan et al., 2018). In this paper, these substrates demonstrated to be antifungal but not to be completely biocompatible by exhibiting some dose-dependent cytotoxicity. Finally, in 2020, the research group (Figure 4d) used nucleophilic substitution reactions to form urea and pyridine-containing chitosan, and these polymers also proved to be antifungal and also to cause low cytotoxicity on L929 cells with cell viabilities up to 100% (Zhang et al., 2020). For the last two examples, not only antifungal activity was achieved, but also antioxidant and radical scavenging properties. Although these advances are not specifically for human relevant fungi, they showed progresses in pathways to obtain functional antifungal substrates for human use in the future.

Although many of the recent advances on the development of antifungal substrates have been performed onto chitosan, other polymers have also exhibited good activity. For example, another important field for antifungal cationic polymers are derivatives of nylon-3 which are produced by ring-opening polymerization of \(\beta\)-lactams which general structure is depicted on Figure 5. It is important to mention that most of the examples presented in this work involve the synthesis of specially crafted monomers (via chemical modification of the monomers or specialized synthesis of specific monomers) to form systems that could be antimicrobial or even could have other functionalities. However, as with any polymeric system modification, post-polymerization is also possible and may be useful in certain cases (Liu et al., 2014).

These polymers are interesting since they mimic the underlying structures of naturally occurring peptides that aid in the immune response against microbes. However, they lack \(\alpha\)-peptide bonds cleavable by natural enzymes coming from some antifungal resistant pathogens. This kind of polymers originally showed good response against bacteria without being toxic to human cells. With further developments, other polymer structures were also found to be toxic to fungi without compromising their biocompatibility. One of the first examples of such systems was produced in 2013, where custom amino-containing \(\beta\)-lactams were copolymerized by anionic ring-opening polymerization to form racemic mixtures of poly-\(\beta\)-peptides (Zhang, Kissounko, et al., 2009). In this work, the produced nylon-3 derivatives were capable of inhibiting the growth of \(C.\) albicans with MICs as low as 3.1 mg/L and \(HC_{10}^2\) and \(IC_{10}^3\) higher than 400 mg/L for the corresponding polymer. This evidences a very good antifungal activity and very low cytotoxicity. Interestingly, these polymers

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**TABLE 1** MICs and MFCs for pyridine modified chitosan (Jia et al., 2016)

| Microorganism   | Chitosan MIC (mg/L) | Chitosan MFC (mg/L) | N-(1-carboxybutyl-4-pyridinium) chitosan MIC (mg/L) | N-(1-carboxybutyl-4-pyridinium) chitosan MFC (mg/L) |
|-----------------|---------------------|---------------------|---------------------------------------------------|---------------------------------------------------|
| *Botrytis cinerea* | 0.25 8.00           | 0.13 4.00           | 0.25 2.00                                         | 0.13 1.00                                         |
| *Fulvia fulva*   | 0.25 2.00           | 0.13 1.00           |                                                   |                                                   |

\(^1\)MIC: Minimum inhibitory concentration. For antimicrobial substances, is the minimum concentration of said substance in solution capable of visibly inhibiting the growth of a pathogen.

\(^2\)MFC: Minimum fungicidal concentration: For antifungal substances, is the minimum concentration of said substance in solution capable of killing at least 99.9% of the initial pathogens in a culture medium.

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**FIGURE 3** Synthetic route for N-(1-carboxybutyl-4-pyridinium) chitosan chloride

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**FIGURE 4** A variety of examples for the modification of chitosan, where the research group (a) used azide–alkyne click reactions to include quaternary ammonium onto chitosan (Tan et al., 2018). In this paper, these substrates demonstrated to be antifungal but not to be completely biocompatible by exhibiting some dose-dependent cytotoxicity. Finally, in 2020, the research group (Figure 4d) used nucleophilic substitution reactions to form urea and pyridine-containing chitosan, and these polymers also proved to be antifungal and also to cause low cytotoxicity on L929 cells with cell viabilities up to 100% (Zhang et al., 2020). For the last two examples, not only antifungal activity was achieved, but also antioxidant and radical scavenging properties. Although these advances are not specifically for human relevant fungi, they showed progresses in pathways to obtain functional antifungal substrates for human use in the future.

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were also very effective antibacterials having MICs for *E. coli*, *B. subtilis*, *E. faecium* and *S. aureus* ranging from ~100 mg/L to ~102 mg/L (Liu et al., 2013). On a follow-up study, Liu and collaborators determined some of the crucial structural components necessary for these compounds to be useful, related to the β-peptide structure, the cationic and hydrophobic balance and how this is related to toxicity against *C. albicans* and some other fungi (Liu et al., 2014).

From these pioneering works, more studies emerged in which different nylon-3 derived copolymers were studied. On one of these studies, the evaluated nylon-3 derivative showed excellent antifungal activity against several organisms from the genera *Candida* and *Cryptococcus*, comparable to fluconazole and amphotericin B (AmB) (Rank et al., 2017, 2018), even showing synergism when used along these antifungals. Unfortunately, these substrates were not effective against *Aspergillus* spp by themselves, but they were shown to enhance the effect of otherazole antifungals such as posaconazole and itraconazole against these pathogens. Finally, for this work, the cytotoxicity of the compounds was evaluated and it was concluded that these compounds are still biocompatible up to doses much higher than the determined MICs (Rank et al., 2017). In a follow-up study, the same research group evaluated new derivatives of these compounds obtaining an extensive list of inhibition interactions within several genera of fungi (Rank et al., 2018).

A last notable example of effective antifungal cationic polymers is a member of the well-known guanidines used as antiseptics and antimicrobials in wound dressings, contact lens solutions, gloves, etc. (Ali & Wilson, 2017; Kariduraganavar et al., 2014; Lee et al., 2004; Lim et al., 2008; Niu et al., 2017). In this work, polyhexamethylene guanidine hydrochloride (PHMGH) was evaluated for its

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**FIGURE 4** Modified derivatives of chitosan which have shown potentiated antifungal properties (Tan et al., 2017, 2018; Wei et al., 2018; Zhang et al., 2020)

**FIGURE 5** Formation of nylon-3 derivatives from ring-opening polymerization of substituted β-lactams

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**Substituted β-lactam**

**Substituted Nylon-3**

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antifungal properties (Figure 6). The authors found that this polymer has comparable MICs to AmB against various fungi species (Table 2), while causing no haemolysis or LDH release at concentrations at least up to 16 times higher than the found MICs (in direct contrast with AmB which is much more toxic to human cells). Additionally, in this work, they elucidated a possible mechanism for its antifungal behaviour which was determined to be pore formation and ion leakage form the cell (Choi et al., 2017). Additional studies regarding both low-molecular weight and polymeric guanidino compounds as antifungals have also shown promising results (Buxbaum et al., 2006; Jana et al., 2005; Manetti et al., 2009). Developments performed on this kind of substrates will represent promising alternative as novel cationic antifungals.

2.2 | Azoles

Azole antifungals are one of the most important developments of the last century in antifungal therapy. Prior to the development and introduction of this new generation of drugs, the majority of therapies against fungal infection implied aggressive side effects and toxicity (Refer to section regarding polyene macrolides). Therefore, ‘classic’ antifungals, like ketoconazole, fluconazole, clotrimazole, miconazole, itraconazole, voriconazole and posaconazole, all contain an azole in their structures (Allen et al., 2015). Generally, most of these drugs work by inhibiting important metabolic processes of the fungi organisms, such as the production of ergosterol (which is an essential component of fungi cell walls). Therefore, the introduction of these functional groups to polymers has been a recently explored alternative in the field of antifungals. It is important to mention that although these heterocyclic moieties are clearly identified as being effective antifungals, since these heterocyclic functional groups may be alkylated or protonated to form quaternary ammonium salts, they have also been explored as antibacterial materials due to their positive charge (Anderson & Long, 2010; Andersson Trojer et al., 2013; López-Saucedo et al., 2017, 2018; Meléndez-Ortiz et al., 2015, 2016; Yang et al., 2018). In this section, we only present examples of azole-containing polymers which have shown to be effective against fungi. We were interested in presenting azoles on their own section because these functional groups have proven to be very effective as antifungal drugs with minimal side effects and since their mechanism of action is not only due to electrostatic interactions as in the case of cationic antifungals.

![Polyhexamethylene guanidine hydrochloride (PHMGH)](image)

**FIGURE 6** Polyhexamethylene guanidine hydrochloride (PHMGH)

| Microorganism | MIC (mg/L) |
|---------------|------------|
|               | PHMGH | AmB |
| C. albicans (ATCC 90028) | 1.25 | 2.5 |
| C. parapsilosis (ATCC 22019) | 1.25 | 2.5 |
| M. furgur (KCTC 7744) | 2.5 | 2.5 |
| T. beigelli (KCTC 7707) | 1.25 | 1.25 |
| T. rubrum (KCTC 6345) | 2.5 | 1.25 |

A first example of polymers containing an imidazole group as antibacterial and antifungal substrate is a 2019 patent in which a series of imidazole ionenes showed to be effective antibacterial and antifungal agents with no significant haemotoxicity (WO 2019/088917 A1, 2019). In 2019, Wei and collaborators obtained different cationic chitosan derivatives through the inclusion of imidazole derivatives bounded to oxygen number 6 of the chitosan structure (Figure 7). These derivatives were demonstrated to have antifungal activity against Botrytys cinera and Gibberella zeae with good biocompatibility to human HaCaT cells (Wei et al., 2019).

Chun’s group has modified polymers with azole groups to add antifungal properties. For example, in 2018, crosslinked polyurethanes (PU) containing imidazole groups were obtained by grafting and crosslinking 4-imidazole acrylic acid using AIBN as an initiator (Figure 8). These polymeric materials were tested for their antifungal properties as well as for their mechanical properties and shape-memory capabilities. Films of this materials were shown to have the ability to attain shape recovery due to the introduction of increasing amounts of the imidazole moiety in the crosslinked structure. Additionally, these films were able to have flexibility even at low temperatures (<10°C) due to the grafting of the imidazole. Finally, some of these materials were demonstrated to be antifungal against a mixture of C. globsosum, A. niger, P. pinophilum, G. vires and A. pullulans (Chung, Kim, et al., 2018).

In addition, the same group modified PU with benzimidazole rings, since benzimidazole avoids fungal growth against a wide spectrum of fungi. The surface modification of this polymer was achieved by a grafting reaction with benzimidazole, 2 hydroxyethyl acrylate and acrylic acid, to increase the hydrophilicity and to facilitate the contact between the fungi and the benzimidazole moiety, see Figure 9. The resulting material showed shape-memory properties with fungi growth inhibition, when tested in a mixture of Aspergillus niger (ATCC 9642), Aureobasidium pullulans (ATCC 15233), Chaetomium globosum (ATCC 6205), Gliocladium virens (ATCC 9645) and Penicillium pinophilum (ATCC 11797) (Chung, Park, et al., 2018).

A final example of azole-containing polymers was the inclusion of three (triazole) and four nitrogen (tetrazole) rings to produce polymer pipes, which are resistant to corrosion due to bacteria or fungi. For this objective, the authors modified low density polyethylene (LDPE) films with various triazoles and tetrazoles through extrusion. With these, the authors demonstrated significant antifungal activity against Aspergillus niger, Penicillium
cyclopium and Trichoderma spp. fungi. Although this work was originally envisioned as an anticorrosive additive to pipes, polymeric materials such as LDPE are very common on medical devices, and thus, the application of multinitrogen rings onto polymers may be a viable solution for antifungal polymers in the future (Tsarenko et al., 1998).

3 | Fungicide Addition to Polymers

In contrast to intrinsic antifungal polymers or macromolecules, some polymers used in medical devices have been doped or modified by the addition of well-known antimicrobial agents, including antibacterial, antifungal and biocidal compounds. The addition of this kind of compounds into polymers has been employed mainly with the aim of avoiding bacterial adhesion, and thus preventing the contamination of medical devices such as catheters and valves. There are several studies on the synthesis of drugs to prevent fungal biofilm formation, since it causes health hazards (Costa-Orlandi et al., 2017; Desai et al., 2014).

There are at least three ways to provide antifungal properties to polymers by adding organic or inorganic fungicides: first, formation of fungicide/polymer composites or blends, second, covalent attachment of fungicide moieties in the polymeric structure and third, use
**FIGURE 9** Benzimidazole-AAc grafts onto polyurethane surface (Chung, Park, et al., 2018)

**FIGURE 10** Incorporation of fungicides into polymers for biomedical applications. (a) Blends and composites, (b) Micelles and nanoparticles and (c) Grafts onto polymer surface and (d) Polymers with fungicide as pendant group
of polymeric micelles and nanoparticles for fungicide retention and release.

The most common of the three methods is mixing both components to obtain a polymer/fungicide composite or a simple mixture or blend (Figure 10a). This approach has allowed the formation of controlled-release systems such as micelles or polymer nanoparticles (Figure 10b). In these two methods, the fungicide is attached, loaded or immobilized by non-covalent interactions with the polymer matrix. In another method, the active compound can be attached via covalent bond by conventional chemical reactions, such as nucleophilic substitution or condensation reactions. The resulting material usually shows antifungal activity due to the active compound. The modification can be performed onto the surface of a polymer (Figure 10c) or in other polymers and hydrogels (Figure 10d).

Although this kind of modifications is less effective than the use of intrinsic antifungal polymers (especially cationic polymers), this approach is extensively used in the development of antifouling polymeric surfaces and for the synthesis of fungicide delivery systems. These fungicides can be metallic nanoparticles, metal cations, organic compounds such as polyenes,azole rings and lipopeptides, among others. Firstly, in this section, we will review the metal-loaded polymers and composites.

3.1 | Metal-loaded polymers and composites

Metal-nanocomposites with nanoparticles (NP) embedded into polymeric matrices have been developed during the last two decades due to their good antimicrobial properties in medical devices, food-packing and other applications in which sterile coatings are needed (Hanemann & Szabó, 2010; Jaramillo et al., 2019; Muñoz-Escobar & Reyes-López, 2020). The most common metals studied as NP embedded into polymeric matrices are Ag, Cu and Zn. Their antimicrobial properties are function of cation identity, cation controlled-releasing properties as well as selectivity to the target cells (Tamayo et al., 2018). Regarding the pathways of metal toxicity, the main mechanisms described in the literature for silver NPs are Ag⁺ binding to proteins which produces changes in the cell wall and their metabolism as well as the binding to nitrogenous bases of DNA and RNA. Additionally, CuNPs and AgNPs can produce oxidative stress by the formation of ROS species (Akter et al., 2018; Vazquez-Muñoz et al., 2017). Furthermore, it is generally accepted that although most of the research has been developed for their effects on bacterial growth, the mechanisms are similar for the inhibition of fungi species (Vincent et al., 2018).

Antifungal coatings against Saccharomyces cerevisiae yeast have been reported using CuNPs loaded into water-insoluble polymeric matrices of polyvinylmethylketone (PVMK), polyvinylchloride (PVC) and polyvinylidenefluoride (PVDF). With a surface metal loading of 1%-2% and NP diameter of 4.6 nm ± 1.8 nm, the composite CuNP-PVMK displayed the strongest antifungal activity since no CFU/ml was observed. In an additional experiment, the antifungal activity of CuNP-PVMK was correlated as a function of seven different CuNPs loadings, thus indicating interesting controlled-release properties for spinnable bioactive coatings (Cioffi et al., 2004). The same authors made improvements of the CuNP-PVMK composite by CuNPs electrochemical stabilization into the polymeric matrix to minimize the damage for untargeted cells, improving controlled-releasing properties thorough formation of Cu-NPs clusters of about 500 particles (Cioffi et al., 2005).

Polycaprolactone (PCL) is one of the most used polymers in biomedical applications due to its biodegradability and biocompatibility (De Paula et al., 2018). Recent studies have explored PCL fibres as loading matrices for CuONPs (average size 35 nm) against fungi components of oral candidiasis: C. albicans, C. glabrata and C. tropicalis. The CuONPs showed increased diameter (90%) in the composite nanofibres (PCL-CuONPs). The CuONPs were loaded from solutions with 1 to 100 nM initial concentrations, and the evaluation of their antifungal activity was carried out with EUCAST protocol, showing a marked antifungal activity against all tested Candida species at initial concentration of 25 nM of CuONPs. Apoptotic cell death was the main pathway observed, caused by the rupture of the cell wall and was attributed to the Cu²⁺ leaching in the biological environment. This study remarkably underlined the effect of pH, ionic strength and dissolved organic matter in the displayed toxicity by the leaching of CuONPs (Muñoz-Escobar & Reyes-López, 2020).

Oral diseases (e.g. denture stomatitis) caused by C. albicans in denture prosthetics have shown resistance against conventional antifungal agents and thus have become an issue in the dental area. To mitigate this, the development of a new antifungal polymeric agent consisting of AgBr-NPs loaded into quaternary ammonium salt polymer 4-vinylpyridinium (NPVP) and then mixed with polymethylmethacrylate (PMMA) denture resin has shown an inhibitory effect on the growth of C. albicans. The composite AgBr-NPVP was mixed at 1% concentration with PMMA to get (after dilutions) concentrations ranging from 0.1% to 0.5% of the metal agent mixed within the resin. With this procedure, the AgBr-NPs (average size 30 nm) were embedded into the cationic NPVP. The MIC reported was 250 µg/ml and was obtained in a culture medium using artificial saliva. A correlation between loaded Ag-NPs and the antifungal activity was found, showing controlled-release properties for this system (Zhang et al., 2017).

AgNPs in binary nanocomposites Ag@Fe₃O₄ and Fe₂O₃@Ag in which non-cytotoxic polyacrylate (relative mass = 8,000 g/mol) was used as a spacer between AgNPs and the oxide particles showed both antifungal and magnetic properties. These features are promising for drug delivery applications where an antimicrobial agent could be targeted and removed by an applied external magnetic field (Prucek et al., 2011). Interestingly, the polyacrylate spacer suppresses most of the interparticle interactions. The composite Ag@Fe₃O₄ (AgNPs average size 70 nm) showed lesser antifungal activity compared with the nanocomposite Fe₂O₃@Ag (AgNPs average size 5 nm), this is in line with the known correlation between antimicrobial properties of AgNPs and the NP size (Baker et al., 2005). The reported MIC values against four Candida species were from 1.9 mg/L to 31.3 mg/L.
Composites of AgNPs with chitosan (from crustacean waste) have been synthesized to avoid agglomeration of nanoparticles (Kalavani et al., 2018). Amino groups in chitosan were proposed to be acting as ligands for stabilizing the spherical NPs with size ranging from 10 to 60 nm. The chitosan-AgNPs showed antifungal activity towards A. niger (inhibition zone 15 mm), A. fumigatus (13 mm), A. flavus (13 mm) and C. albicans (11 mm). The results observed in the characterization of the NPs by FTIR showed that the primary amino groups of chitosan were involved in the interaction with AgNPs’ surface; thus, chitosan is acting as a capping site within the AgNPs composite, as indicated by the increasing AgNPs size with a decrease in chitosan initial concentrations. In this work, the authors concluded that crustacean waste (chitosan) represents a cheaper source to produce small AgNPs for medical applications.

Graphene oxide (GO) has also been used to get Ag nanoparticle-stabilized systems. The composite (PVA/GO-AgNPs) in which GO surface has been decorated with AgNPs (average size 3.1 nm) and then incorporated as a reinforcing filler into poly(vinyl alcohol) (PVA) matrix. PVA has been used for its biocompatibility, biodegradability, low toxicity and its mechanical properties. The composite showed antimicrobial properties and promising use in wound healing as well as infection prevention (Cobos et al., 2020).

Bandage material cotton fibres (cellulose) have also been the target of several works on nanocomposites. Cotton fibres have been covered with bimetallic NPs of composition Ag/Cu 1:1, forming composites with high antimycotic properties. The composite fibre with Ag/Cu NPs 0.06%–0.25% w/w showed high antifungal activity against C. albicans. Interestingly, the AgNPs coated cotton fibres did not show antifungal properties but only antibacterial proliferation. The antimycotic properties did not change after washing, and the preparation method is highlighted because cotton fibres are just immersed in water solutions of AgNO3 and CuSO4 by 30 min and subsequently ironed. The antifungal activity remains after 6 months (Mathew & Kuriakose, 2013).

Nowadays, zinc oxide nanoparticles (ZnONPs) are also considered viable as antimicrobial substrate due to their potential antifungal properties, are registered as ‘Generally Recognized as Safe’ (GRAS) by the FDA and have several promising applications (e.g. drug delivery and antiseptic properties). The pathways of actions for antimicrobial and antifungal properties are currently not completely understood, but it is generally accepted that they displayed multimodal activity (ROS mediated and zinc direct effects) (Cierech et al., 2016; Roy Choudhury et al., 2017). As an example of this, a composite of ZnONPs (30 nm diameter) coated with chitosan-linoleic acid has been reported to show antifungal properties against C. albicans comparable to that of fluconazole. The MIC shown by the composite is 32 mg/ml vs 8 mg/ml for fluconazole. The chitosan-coated with ZnONPs has a higher inhibitory activity than the chitosan itself in antifungal biofilm formation; thus, the composite is proposed as a novel agent for decreasing the adhesion capacity of C. albicans (Barad et al., 2017).

Packaging films using agar as polymer matrix are used due to their flexibility and transparent properties both in the food industry and in biomedical devices. It has been demonstrated that ZnO-agar composite at 2%–4% (w/w) enhances the antifungal properties of fruits wraps showing promising features in biomedical applications (Kumar et al., 2019).

Aflatoxins produced by moulds such as Aspergillus flavus are mutagens with important clinical implications that grow in soils and grains. Appropriated films to inhibit their growth have been reported by using poly lactic acid (PLA) as a matrix and layered with ZnONPs from 1% to 5%. The composite films were tested for antifungal activity against Aspergillus flavus and Aspergillus parasticus showing an inhibitory effect as the percentage of ZnONPs increases (Nasab et al., 2019).

The development of novel materials for metallic prosthesis in orthopaedic surgeries presents challenging problems concerning the antifungal properties of the materials. Titanium surfaces are prone to the formation C. albicans films (Dhir, 2013), and biocompatible materials such as hydroxyapatite (HAp) are not the exception (Ciucu et al., 2016). Interestingly, composite materials based on titanium as the substrate and coated with poly(dimethyl siloxane) (PDMS) have been reported as matrices for layering with doped hydroxyapatite. The composite AgHAp-PDMS displayed the strongest antifungal activity, and the observations showed a strong decrease of the biofilm (C. albicans) and almost total disappearance after 48 and 72 hr. On the other hand, ZnHAp-PDMS composite showed just a slight decrease of the fungal cells’ biofilm (Groza et al., 2016).

3.2 | Addition of organic-fungicide compounds to polymers

As it was mentioned previously, another approach to provide antifungal activity to a polymer is attaching the organic compound via covalent bond to the polymer chains. Commonly, the active compound can be added in two ways: first, the compound is grafted to the polymer by conventional chemical reactions, or second by the synthesis of the fungicide monomer, sometimes a vinyl moiety is added to the compound structure and then polymerized. The approach of covalent binding of the active compound to the surface may achieve prolonged action against fungal adhesion to the biomedical device (Costa et al., 2011; Yu et al., 2019).

The covalent immobilization of lipopeptides onto polymers has been tested to avoid the formation or to defeat existing biofilms; this procedure has been achieved by several chemical treatments of polymers with the antifungal drugs (Alves & Olivia Pereira, 2014; Coad et al., 2015; Griesser et al., 2015; Kuchariková et al., 2016). The fungicide caspofungin was coupled using a conventional bimolecular nucleophilic substitution benefiting from the primary amines in its structure. A promissory polymer for antifungal coatings made of allyl glycidyl ether polymerized by plasma treatment was functionalized via the spontaneous reaction between amine and epoxide groups on the surface, as can be seen in Figure 11. Caspofungin-grafted polymers were very efficient against the two fungal pathogens C. albicans and C. glabrata; additionally, the materials showed...
biocompatibility (Michl, Giles, Cross, et al., 2017). More recently, caspofungin has been grafted onto polymethacrylates (Alex et al., 2020) such as poly(2-hydroxyethylmethacrylate) (PHEMA) (Michl, Giles, Mocny, et al., 2017) for antifungal activity against *Candida* and *Aspergillus* species.

According to mixtures or composites, there are reports of polymeric surfaces coated with fluorocarbon (CF₄) films and deposited by ion plasma technology. In these reports, polyethylene terephthalate (PET) was treated with CF₄ via plasma, and when the fluorine-containing got over 60%, the fungi stopped growing, showing high efficacy (Elinson et al., 2018).

Other polymer/fungicide-clay nanocomposite was prepared for their antifungal activity. First, a mixture of montmorillonite and terbinafine hydrochloride (OMMT) was obtained by solution intercalation; subsequently, the OMMT was mixed with poly(dimethyl siloxane) (PDMS) to get a composite with the fungicide. These nano-composites were tested for antifungal activity against *Candida albicans* which strongly inhibited the fungus growth in a plate (Meng et al., 2009).

Other fungicides, such as carbendazim (a benzimidazole derivative), have been supported on poly(ethylene-co-vinyl alcohol) and epoxy resin to provide antifungal capacity to the polymer surface, and the resulting polymers demonstrated to be effective against *Aspergillus fumigatus* and *Penicillium pinophilum* (Park et al., 2001).

Finally, antifungal hydrogels have been investigated (AbouSamra et al., 2019; Liu et al., 2019; Zumbuehl et al., 2008). For example, a thermo-responsive hydrogel was loaded with an antifungal living bacterium. In 2018, Lufton et al. made a formulation of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) and *Bacillus subtilis*, since this bacterium efficiently produces and secretes potent antifungal compounds. The authors used this formulation against *C. albicans* and demonstrated similar antifungal activity as that of ketoconazole. The use of a hydrogel with a lower critical solution temperature (LCST) around body temperature allows its administration through skin, which is useful for fungi skin infections (Lufton et al., 2018).

### 4 | DRUG DELIVERY SYSTEMS

Nowadays, there are several investigations about new fungicide delivery systems made out of polymers and the modification of polymers to avoid the problem of hospital-associated infections and contamination of the medical materials (Howard et al., 2020).

The use of micelles for drug distribution and releasing has been employed since they favour the administration of water-insoluble drugs. Polymeric micelles with an amphiphilic structure allow the complexation of some drugs in the hydrophobic core. The hydrophilic section of the structure can interact with the human cells decreasing cytotoxicity and therefore improves the biodistribution through the body. The mechanism of action (release) of any micelle system depends directly on the compatibility between the drug and the core, which is closely related to the chemical nature of the polymer used, molecular weight and particle size (Kulthe et al., 2012).

Studies report polymeric micelle systems or nanoparticles for fungicide retention and controlled release. Additionally, some of them tried to decrease the side effects and toxicity of the orally drug administration, enhance their pharmacokinetic profile and improve the frequency of doses (Souza & Amaral, 2017). One of the most used is the amphotericin B (AmB) due to its broad-spectrum antifungal activity and its biphasic behaviour, which allows the complexation via non-covalent interactions with almost any polymer when controlling the chemical structure. This versatility has allowed the synthesis of new polymeric systems for AmB releasing, decreasing its cytotoxicity (as it will be referred in the section dealing with polyenes and echinochandins).

Polymer nanoparticles, micelles and nanocarriers have been employed for AmB encapsulation and have been tested as controlled delivery systems driven by diffusion for systemic or localized fungal infections, systemic or through the skin. For example, AmB has been loaded into polycarbonate micelles functionalized with donor-acceptor hydrogen bond groups. In 2016, Wang *et al.* added phenylboronic acids (B) and urea (U) as pendant groups in PEGylated-polycarbonate chains to form micelles and to keep AmB...
molecules inside attached by hydrogen bond and other non-covalent interactions. The chemical nature of the pendant groups allows micelle formation, as represented in Figure 12.

The above-mentioned micelles were formed using either urea- and boronic acid-modified polycarbonate or both. The best performance was shown by two micelles, the B-modified and the mixed (U + B). The release of AmB in sink conditions after 24 hr reached almost 50% and 60%, respectively. In addition, the in vitro essays showed similar inhibition to free AmB (Fungizone®) against C. albicans. Moreover, these AmB-release systems showed low nephrotoxicity and low haemolytic degree (Wang et al., 2016).

This kind of micelle-type drug delivery systems has been developed with many different polymers and fungicides. For instance, block copolymers of poly(ethylene oxide) (PEO) and poly(amino acids) have demonstrated to be effective against some fungi, such as C. albicans. Additionally, they showed low haemolysis compared with conventional antifungal drugs and the antifungal activity was four to eight times higher than Fungizone® in terms of minimal inhibitory concentrations (MICs) (Yu, Okano, Kataoka, & Kwon, 1998; Yu, Okano, Kataoka, Sardari, et al., 1998).

In 2003, Kwon’s group developed polymeric micelles for AmB retention, and Adams et al. used aspartic acid derivatives to form micelles with encapsulation of the fungicide. Conveniently, the controlled release decreased the toxicity of AmB and the loaded micelles inhibited fungal growth (Adams et al., 2003; Adams & Kwon, 2003; Lavasanifar et al., 2002).

In another example, PEO and polyethylene glycol (PEG) were combined with several polymers such as polystyrene (PS) as block copolymers to form micelles and retain AmB (Kun Han et al., 2007) and poly(ε-caprolactone)/retinol. Both systems showed good efficacy against common Candida species; moreover, the second one demonstrated improved antifungal efficiency against C. albicans and C. auris strains compared with Fungizone® rather than the PS copolymer (Rodriguez et al., 2020).

Additionally, polysaccharides have been used with the same purpose, as it was mentioned in the section dealing with cationic polymers, chitosan is widely used for antimicrobial and biocompatibility applications. Cross-linked chitosan/porphyrin (CS/POR) polymer nanoparticles were useful for AmB encapsulation, and different ratios of the components were tested. The particle size varied between 100 and 360 nm, and all of them proved to inhibit the growth of C. albicans and three Aspergillus spp. The most effective system was the CS/POR-AmB without a crosslinking agent, showing the lowest half-maximal inhibitory concentration (IC50) against four fungi species (A. fumigatus, A. niger, A. flavus and C. albicans). They even resulted more effective than the conventional fungicides with AmB as active substance (Bhatia et al., 2014). Also, CS-dextran sulphate nanoparticles have been used for AmB loading (Tiyaboonchai & Limpeanchoke, 2007). Another study used polycyclodextrins and dextran to keep AmB in the microscale with antifungal activity against the common yeast Saccharomyces cerevisiae (Haley et al., 2019).

AmB has also been loaded in D-α-tocopheryl polyethylene glycol 1,000 succinate and poly(ε-caprolactone-ran-glycolide) nanoparticles with activity against C. albicans; PDMAEMA-b-PCL-b-PDMAEMA nanocarriers with reduced haemotoxicity and antifungal activity against three Candida species, C. albicans, C. krusei and C. glabrata and, finally in poly(α-glutamic acid) and polyrotaxanes (Diaz et al., 2015; Mohamed-Ahmed et al., 2013; Tang et al., 2014; Zhang, Ke, et al., 2009).

Natamycin, an antifungal polyene, has been loaded in self-assembled poly(ethylene glycol)-block-poly(glycidyl methacrylate) (PEG-b-PGMA) micelles, the delivery process is more prolonged than the pure natamycin, and thus, it can be used as a controlled delivery system with better pharmacokinetic profile and low cytoxicity when being tested in corneal epithelial cells. Additionally, the natamycin-loaded micelles required lower doses for the same activity compared to pure natamycin and a decrease in the dose frequency due to the prolonged release profile (Guo et al., 2020).

Recently, stimuli-responsive polymers have been employed to immobilize azole fungicides and avoid C. albicans biofilms formation with a reduction of the biomass (>50%). For example, in 2020, Albayat and collaborators developed pH-responsive micellar systems based on poly(ethylene glycol) ethyl ether methacrylate (PEGMA) and poly(2-diethylamino) ethyl methacrylate (PDEAEMA) leading to block copolymers P(PEGMA-b-DDEAEMA) loaded with iraconazole. PDEAEMA has a tertiary amine which is sensitive to pH changes, and the fungi biofilms tend to acidify the zone, thus

**FIGURE 12** PEG/PC-B micelles with AmB encapsulation (Wang et al., 2016)
triggering the drug release as a consequence of the repulsive charges of the protonated amines (Albayaty et al., 2020).

5 | POLYENE MACROLIDES AND ECHINOCANDINS

Polyene macrolides are a series of very powerful broad-spectrum antifungals which are often used to treat moderate to serious fungal infections. The structures of the two most important examples of this kind of macrocyclic/polymeric antifungals are shown in Figure 13, Amphotericin B (AmB) and Nystatin which are both obtained from biosynthetic pathway (Tevyashova et al., 2013).

The main structural feature of these drugs is that the macrocycles contain various conjugated dienes. These molecules are often the preferred agents when dealing with serious fungal infections and are often administered to immunocompromised patients to stop infections after organ transplant or severe radiation treatment.
Although these drugs are highly effective, they have the disadvantage of not being selective to fungi cells and are often toxic to mammal cells. The mechanism of action of AmB starts with binding of the drug with ergosterol on fungi cell walls, following leakage of ions due to pore formation on the cell walls and finally killing the pathogen.

AmB is often toxic to mammal cells since the structure of cholesterol is similar to ergosterol, which causes binding of AmB to mammal cells (see Figure 14). Therefore, these drugs also tend to affect the kidneys, liver and central nervous system of patients; this is an important concern for AmB (Borowski, 2000; Tevyashova et al., 2013).

Since these drugs have been prescribed since the 1950s, incremental doses are often needed to combat resistant fungi, increasing the concern for ineffectiveness and aggressive side effects. However, these drugs are still very useful since they are antifungals which are the least prone to increase fungi resistance (although as mentioned before, they are not exempt of generating this undesired effect). Due to the advantages and the effectiveness of these antifungals, new derivatives of AmB and Nystatin have been developed during the last decades. These modifications have been performed by direct chemical modification of the polyene macrolides or by bioengineering the organisms that produce them naturally. Since this comprise only modifications of existing macrocyclic compounds mostly through biochemical means, and not the synthesis of new polymers, this review will only cover two recent representative examples of these modifications due to the importance of these compounds. However, if the reader is interested in a more thorough analysis of this kind of antifungals, we encourage to look on the following references which include current research and existing reviews on the topic (Caffrey et al., 2008; Jarzebski et al., 1982; Kim et al., 2017; Ojika et al., 2003; Qi et al., 2015; Solovieva et al., 2011; Tevyashova et al., 2013).

A chemical modification of AmB is presented as the first example. It is important to mention that this route is not usually the preferred one to modify polyene macrolides because since compounds are usually sensitive to both acidic and alkaline conditions and have poor solubility (Solovieva et al., 2011). In this particular work, a modification of the amine group of the mycosamine portion of AmB was performed by reductive amination of aldehydes of pure and esterified AmB (carbon C-16) with yields between 20% and 76%. MICs were obtained as low as 0.020 mg/L for some of the modified compounds (AmB MIC: 0.3 mg/L), while attaining higher
| Antifungal polymer                                      | References                                                                 |
|--------------------------------------------------------|-----------------------------------------------------------------------------|
| Chitosan modifications                                 | Jia et al. (2016)                                                          |
|                                                        | Tabriz et al. (2019)                                                        |
|                                                        | Tan et al. (2017)                                                           |
|                                                        | Wei et al. (2018)                                                           |
|                                                        | Tan et al. (2018)                                                           |
|                                                        | Zhang et al. (2020)                                                          |
| Nylon-3 derivatives                                    | Liu et al. (2014)                                                           |
|                                                        | Rank et al. (2017)                                                          |
|                                                        | Rank et al. (2018)                                                          |
| Guanidine derivatives                                  | Choi et al. (2017)                                                          |
|                                                        | Buxbaum et al., (2006); Jana et al. (2005); Manetti et al. (2009)           |
| Azoles covalently embedded onto polymers               | WO 2019/088917 A1 (2019)                                                   |
|                                                        | Wei et al. (2019)                                                           |
|                                                        | Chung, Kim, et al. (2018)                                                   |
|                                                        | Chung, Park, et al. (2018)                                                  |
|                                                        | Tsarenko et al. (1998)                                                      |
| Metal-loaded polymers and composites                   | Cioffi et al. (2005)                                                        |
|                                                        | Muñoz-Escobar and Reyes-López (2020)                                        |
|                                                        | Zhang et al. (2017)                                                         |
|                                                        | Baker et al. (2005)                                                         |
|                                                        | Cobos et al. (2020)                                                        |
|                                                        | Mathew and Kurilakose (2013)                                                |
|                                                        | Barad et al. (2017)                                                         |
|                                                        | Kumar et al. (2019)                                                        |
|                                                        | Nasab et al. (2019)                                                         |
|                                                        | Dhir (2013)                                                                |
|                                                        | Ciusta et al. (2016)                                                        |
|                                                        | Groza et al. (2016)                                                         |
| Addition of organic-fungicide compounds to polymers    | Costa et al. (2011); Yu et al. (2019)                                        |
|                                                        | Alves and Olívía Pereira (2014); Coad et al. (2015); Griesser et al. (2015); Kuchariková et al. (2016) |
|                                                        | Michl, Giles, Cross, et al. (2017)                                          |
|                                                        | Alex et al. (2020)                                                          |
|                                                        | Michl, Giles, Mocny, et al. (2017)                                          |
|                                                        | Elinson et al. (2018)                                                       |
|                                                        | Meng et al. (2009)                                                          |
|                                                        | Park et al. (2001)                                                          |
|                                                        | AbouSamra et al. (2019); Liu et al. (2019); Zumbuehl et al. (2008)          |
|                                                        | Lufton et al. (2018)                                                        |
| Antifungal drug delivery systems                       | Wang et al. (2016)                                                          |
|                                                        | Yu, Okano, Kataoka, and Kwon (1998); Yu, Okano, Kataoka, Sardari, et al. (1998). |
|                                                        | Adams et al. (2003); Adams and Kwon (2003); Lavasanifar et al. (2002)       |
|                                                        | Rodriguez et al. (2020)                                                     |
|                                                        | Haley et al. (2019)                                                         |
|                                                        | Diaz et al. (2015); Mohamed-Ahmed et al. (2013); Tang et al. (2014); Zhang, Ke, et al. (2009) |
|                                                        | Guo et al. (2020)                                                           |
|                                                        | Albayaty et al. (2020)                                                      |
| Polyene macrolides and echinocandins                   | Caffrey et al. (2008); Jarzebski et al. (1982); Kim et al. (2017); Ojika et al. (2003); Qi et al. (2015); Solovieva et al. (2011); Tevyashova et al. (2013) |
|                                                        | Kim et al. (2018)                                                           |
|                                                        | Aguilar-Zapata et al. (2015); Debono et al. (1989); Debono et al. (1995); Hashimoto (2009); James et al. (2017) |
| Other antifungal polymers                              | Ahmad et al., (2011)                                                       |
|                                                        | Herzog et al., (2012)                                                       |
|                                                        | Shrestha, Fosso, Green, et al. (2015)                                       |
|                                                        | Shrestha et al. (2015)                                                      |
6 | OTHER ANTIFUNGAL POLYMERS

The previous sections have focused on antifungal polymers classes which share a certain number of characteristics. Nonetheless, some other polymeric antifungal substrates have been found to be individually interesting. In this last brief section, we comment two isolated examples of two systems.

In the first example, we discuss the development of organo-metallic polymer containing tin and produced by the use of hydroxyethyl castor fatty amide oil, a sustainable natural resource. In this work, the formed organometallic polymer (Figure 17) demonstrated inhibition of different strains of C. albicans and even good performance against fluconazole resistant strains. Additional to the antifungal test, ergosterol biosynthesis inhibition was determined for this system, demonstrating that this polymer attacks fungi cells by inhibiting the production of this component of the fungi cell wall (Ahmad et al., 2011).

Another example is a series of studies performed between 2012 and 2015 about amphiphilic tobramycin derivatives as oligomers for polymeric substrates which may act as antibacterial and antifungal agents. Tobramycin is a well-known antibiotic that although is effective against regular bacteria, has started to be ineffective against resistant bacteria. Originally in 2012, this work focused on modifying tobramycin through the formation of amphiphilic long chain structures containing pendant aromatic rings and thioether groups (Figure 18). These compounds were confirmed to be antibacterial against several resistant strains (Herzog et al., 2012). On a follow-up study of this kind of compounds, their antifungal activity was tested against several fungi strains (resistant and nonresistant) of species C. albicans, C. neoformans with MICs as low as 2 mg/L and very low cytotoxicity (Shrestha, Fosso, Green, et al., 2015). In the final study of this series, the use of these new antifungals combined with fluconazole, itraconazole, posaconazole or voriconazole was tested with good results showing synergistic effects between the antifungals (Shrestha, Fosso, Garneau-Tsodikova, et al., 2015).

7 | CONCLUSIONS

Even though antifungal polymers research is a pioneer area compared with the research in antibacterial polymers, the importance of these systems cannot be underestimated since fungi growth is a public health problem; therefore, it is important to find alternatives and new materials with such properties.

In general, new formulations of novel polymeric antifungals such as cationic polymers, azole-containing polymers, polymeric/fungicide mixtures, blends and composites, and modified macrocyclic antifungals have demonstrated to be effective against the most common fungi species including resistant fungi. They have been used not only in medical applications but also as paint additives and as packages in the alimentary industry (Higazy et al., 2010; Hoque et al., 2015; Shemesh et al., 2015). At the same time, the drug delivery systems that have been envisioned for novel and existing antifungals have enhanced the bioavailability and prolonged the fungicide release, driving to decreasing drug ingestion, localized therapy and more convenient administration. At the moment, the research is very active for the production, characterization, testing and future applications of these materials. With further advances on this area, new materials with clinical effectiveness or versatile applications will be produced. As a final reference for the reader, a compilation of current advances is summarized in Table 3.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ENDNOTES

1 Zone of inhibition test: Another way to quantify the antimicrobial effect is to measure the circular zone of inhibition when the material is placed on a petri dish culture containing ~10^6 CFU/ml of a given pathogen.

2 HC10: Concentration of a substance needed for lysis of 10% of human red blood cells.

3 IC10: Concentration of a substance needed for the death of 10% of NIH 3 T3 fibroblasts.

4 Ionene: Polymer which contain ionic groups on the main chain.

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