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Comprehensive insights into the role of nanocarriers in advancing azole-based ocular therapeutics

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Ocular fungal infections pose particularly significant pharmacotherapeutic complications due to the intricate anatomical and physiological features of the eye, which interfere with the efficient delivery of therapeutic agents to targeted ocular areas. Azole derivatives, including imidazoles and triazoles, have been established as a fundamental component in managing these infections due to their broad antifungal spectrum against various causative pathogenic fungal species, such as *Candida*, *Aspergillus*, and *Fusarium*. In contrast, the inefficient physicochemical characteristics, non-selectivity resulting in toxicity, and development of resistance in azole antifungal compounds restrict their effectiveness. This has encouraged research on developing new azole derivatives to overcome these limitations and improve antifungal effectiveness. Focusing on addressing the complex restrictions imposed by ocular barriers and the limitations associated with azole compounds, researchers have been actively developing innovative strategies for ocular drug delivery. These advancements include nanoformulations such as nanoparticles, liposomes, niosomes, nanomicelles, microemulsions, nanoemulsions, nanofibers, and cubosomes, as well as ocular drug delivery devices, including drug-eluting contact lenses, microneedles, and ocular inserts. The article highlights the development of new azole antifungal compounds, along with innovative formulation approaches currently being explored to overcome these barriers, with a particular emphasis on nanoformulations, aiming to improve the management of ocular fungal infections.

1. Introduction

Azoles represent the largest family of antifungal drugs, which are broadly categorized into imidazoles (examples are econazole, tioconazole, ketoconazole, sulconazole, miconazole, *etc.*) and triazoles (examples are voriconazole, itraconazole, fluconazole, posaconazole, *etc.*) based on their chemical structure.[1] Due to their significant biological activity and broad spectrum of antifungal action, azole derivatives have become a fundamental component of pharmacotherapy for invasive systemic fungal infections. The versatility of these antifungal agents extends their application for the management of ocular fungal infections. Over a million individuals worldwide suffer from ocular fungal infections each year, and their prevalence has increased significantly in the past few decades, with fungal keratitis (a corneal fungal infection) having the highest prevalence. Fungal infections affecting the eyelid, orbit, lacrimal apparatus, sclera, conjunctiva, and intraocular components, as seen in cases of fungal endophthalmitis, have also been reported in many instances.[2] These ocular fungal infections are primarily caused by filamentous (*Aspergillus* and *Fusarium*) and non-filamentous (*Candida*) species. Antifungal therapies comprising the polyene, azole, and echinocandin families are widely prescribed for the management of fungal eye infections, with natamycin (a polyene antifungal agent) being adopted as the standard treatment.[3,4]

Antifungal azole derivatives target the ergosterol production cascade by inhibiting the enzyme lanosterol 14-α-demethylase (commonly referred to as CYP51), thereby altering the typical permeability and flexibility of fungal cell membranes.[5] Notwithstanding their strong antifungal properties, the two clinically significant azoles, itraconazole and voriconazole, exhibit concentration-related toxicity and adverse reactions in ocular and invasive systemic fungal infections, despite having a wide spectrum of potent antifungal activity. Fluconazole, on

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the other hand, is considered a more accessible and safer antifungal agent with a low toxicity profile.[6] Since the discovery of this family of antifungal drugs, the azole antifungal class has undergone significant evolution, with each subsequent generation being developed to address particular challenges. In 1944, benzoimidazole was reported as the first azole-based antifungal agent to demonstrate significant fungicidal action. Despite this, the development of an azole derivative agent did not begin until 1958, when chlormidazole was introduced to the market, initiating ongoing research on azole compounds for antifungal treatment. To date, over 40 azole derivatives have been developed as antifungal drugs, which are categorized into four generations based on their structural advancements and antifungal spectrum.[7]

Despite the significant advancements in azole antifungal therapy, these drugs face several limitations in achieving optimal efficacy. One major challenge is the potential development of resistance, particularly with prolonged usage, which primarily targets the drug's intended mechanisms of action. The primary mechanisms involved in the emergence of azole resistance include genetic modifications of CYP51, overexpression, or increased drug efflux by efflux pumps that drive the drug out of fungal cells. Due to increased efflux or inadequate drug-target affinities, several fungal strains exhibit inherent resistance. Furthermore, clinical resistance was triggered by the extensive use of invasive fungal infections for preventive or therapeutic purposes, which remains challenging to identify *in vitro* or *in vivo*. To improve efficacy and overcome various resistance pathways, current research focuses on optimizing azole derivatives and investigating hybrid compounds.[8]

Furthermore, the application of azole antifungal agents for ophthalmic fungal treatment has presented significant challenges, mainly due to the complex anatomical and physiological characteristics of the eye, which comprises several barriers to the efficient delivery of drugs.[9] The majority of azole antifungals have molecular masses that are inappropriate for ocular delivery, poor aqueous solubility due to their high lipophilicity, and other physicochemical characteristics that affect their absorption and penetration through ocular barriers, which in turn impact their ability to target the area of infection within the ocular environment. Moreover, conventional topical formulations often suffer from rapid precorneal elimination due to tear turnover and blinking, resulting in subtherapeutic drug concentrations at the site of infection. These challenges not only compromise therapeutic efficacy but also limit patient compliance and restrict the clinical adoption of azole-based eye drops or ointments. Therefore, addressing these formulation barriers is critical to fully harness the potential of azoles in ocular therapeutics.[10]

The commonly adopted strategy to address the physicochemical limitations of drugs, ocular and systemic toxicities, adverse reactions, and the static and dynamic ocular barriers associated with azole-based antifungal therapies involves the development of novel nanoformulations that have the potential of efficiently delivering drugs to the targeted region of the eye.[11] These advancements include the development of nanosystems, such as nanomicelles, liposomes, nanoparticles, and cubosomes, along with innovative ocular drug delivery devices. These devices have demonstrated improved drug solubility, prolonged retention times, enhanced ocular penetration, and targeted drug delivery to affected ocular tissues. This article aims to provide a detailed insight into the progressions and limitations of azole derivative-based management of ocular fungal infections, and also explain how these challenges are being addressed through the latest developments in nanosystem-based ocular drug delivery platforms. Additionally, this review provides a detailed discussion on the role of functional excipients, such as polymers, chitosan, and stimuli-responsive materials, in enhancing the performance of these nanoformulations.

2. Fungal ocular infections: classification and clinical manifestations

Fungal ocular infections are classified based on the anatomical location of the eye affected, each presenting with distinct clinical features. Ocular infections can occur both around the eye, known as the ocular adnexa (which includes the eyelids, conjunctiva, lacrimal apparatus, and orbital tissues), as well as within the eye itself, affecting the anterior (which consists of the cornea, iris, and lens) and posterior segments (which consists of retina, choroid, and vitreous body).[12] Different types of ocular fungal infections, along with their causing agents, are demonstrated in Fig. 1. Fungal blepharitis is a common ocular surface infection caused by alterations in ocular microbiota, which leads to inflammation in the eyelid margin. Aspergillosis, sporotrichosis, cryptococcosis, blastomycosis, histoplasmosis, and paracoccidioidomycosis are also recognized as types of palpebral infections that can specifically affect the palpebral conjunctiva, the inner lining of the eyelids.[12,13] Infections of the lacrimal duct system, which account for only 0.5% of cases, are relatively rare and can result in endogenous infections of the tear drainage system, including dacryoadenitis, dacryocystitis, and canaliculitis.[14] Ocular orbital infections often arise as a secondary condition involving tissues in the vicinity, including the epidermis, nasopharyngeal cavity, and paranasal sinuses. Periorbital (pre-septal) cellulitis, characterized by infection of anterior to the orbital septum, and orbital (post-septal) cellulitis, which is a more severe infection that occurs posterior to the orbital septum, are the two main categories of inflammatory infections of the eyelids and orbit.[15] Considering its minimal prevalence and ambiguous clinical manifestations, fungal conjunctivitis is a relatively uncommon disorder in ocular treatment, in contrast to other fungal infections of the eye. Fungal conjunctivitis presents a diagnostic challenge, as its symptoms, such as redness, irritation, and discharge, are similar to those associated with bacterial or viral conjunctivitis. In contrast, other fungal eye diseases may be more pronounced and localized.[16]

Furthermore, fungal keratitis (also known as mycotic keratitis or keratomycosis) is characterized by a complex infection and inflammation on the transparent corneal epithelium, as

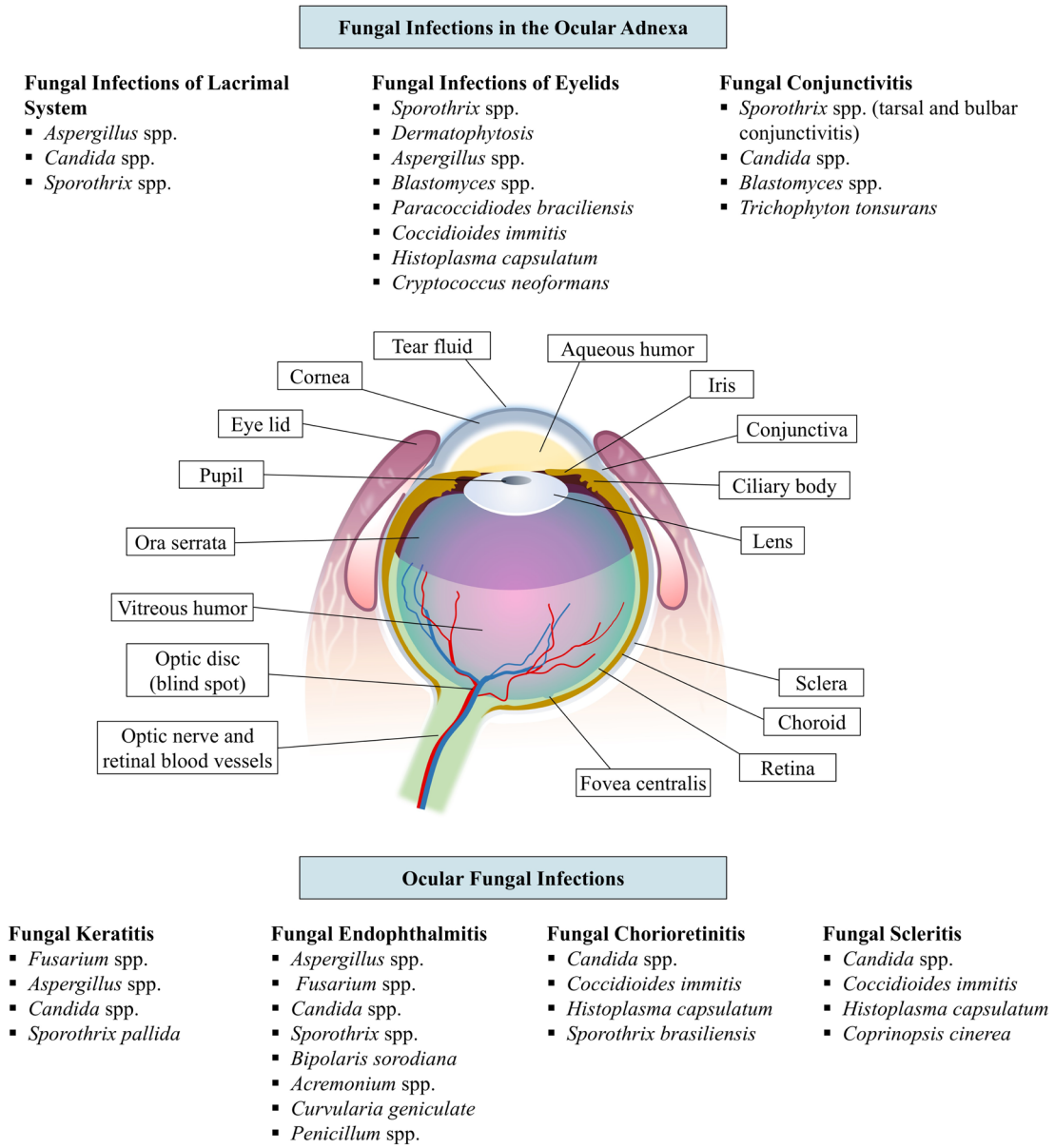

Fig. 1 Anatomical structures of the eye affected by fungal infections and their corresponding etiological fungal pathogens.

well as damage, ulceration, and perforation of the stromal layer of the eye. On the other hand, fungal endophthalmitis represents the fungal infection of the structures inside the posterior portion of the eye that are associated with vitreous and/or aqueous humors. Fungal keratitis is caused by a broad spectrum of filamentous fungi and yeasts, generally, *Aspergillus* spp. and *Fusarium* spp., as well as the yeast *Candida* spp.[17,18] Whilst infections caused by yeast are generally more common in temperate areas, filamentous fungi account for the majority of the infections that occur in tropical and subtropical regions.[19] Fungal endophthalmitis involves intravitreal colonization by microorganisms, which can enter either exogenously, where infecting microorganisms directly inoculate into the eye from outside, like trauma, surgery, or from external ocular infection such as fungal keratitis, or endogenously, where infecting microorganisms enter from inside, through hematogenous spreading.[20] Lastly, profound, localized, white lesions found within the choroid and retina, as well as in the blood vessels and neuronal tissues of the posterior segment of the eye, are the features of fungal chorioretinitis. Unlike other forms of ophthalmic infections that may potentially impact the vitreous fluid, these types of lesions are usually observed with no apparent involvement with the vitreous humor.[13]

3. General management of ocular fungal infections

The primary approach to managing corneal fungal infections is pharmacological, while surgical intervention is considered in cases of progressive, treatment-resistant, or complicated

infections where medical therapy proves insufficient. It is recommended to initiate antifungal therapy only after clinical diagnosis has been confirmed, first by smear examination and subsequently by positive culture results. Topical antifungal therapy remains the primary option for managing ocular fungal infections; however, in severe cases, alternative drug administration routes, such as systemic administration, intrastromal injection, or intracameral delivery, may be employed to enhance drug penetration and therapeutic efficacy.[21]

Since the first FDA-approved topical antifungal medication for ophthalmic use, 5% natamycin is commonly acknowledged as the first-line treatment for fungal keratitis and other ocular fungal infections. It exhibits potent activity, particularly against filamentous fungi, including *Fusarium* and *Aspergillus* species, making it highly effective in superficial keratomycosis. The triazole antifungal voriconazole, which is chemically derived from fluconazole, has broad-spectrum effectiveness against yeasts and filamentous fungi. When administered alone or in combination, topical voriconazole eye drops have been shown to serve as an effective alternative to natamycin in cases of resistance. When the topical ophthalmic formulation of natamycin 5% is ineffective for fungal keratitis, 0.15% amphotericin B eye drops can be a potential alternative for ophthalmic topical administration.[22] Although 0.15% amphotericin B eye drops are recommended as a first-line treatment for fungal infections caused by *Candida* species, they show limited effectiveness against *Fusarium* infections. Randomized clinical trials have shown that 2% econazole eye drops are as effective as 5% natamycin eye drops in managing fungal keratitis, particularly for infections caused by filamentous fungi species. 2% fluconazole eye drops have also been used in combination with other antifungal drugs such as amphotericin B for fungal keratitis therapy.[23] Additionally, 1% clotrimazole is available topically to treat fungal keratitis.[22,24]

In cases of extensive corneal involvement, such as ulcers extending to the limbus, deep stromal keratitis, or those complicated by scleritis or endophthalmitis, systemic antifungal therapy—either oral or parenteral—may be required. Furthermore, systemic antifungal administration is advised as a prophylactic measure following penetrating keratoplasty performed for fungal keratitis to prevent recurrence or postoperative complications.[18] Oral voriconazole, at a dosage of 200 mg twice a day, has good ocular penetration, consistently generating concentrations above the Minimum Inhibitory Concentration (MIC)† for most corneal fungal infections and delivering constant drug levels in ocular tissues. Oral ketoconazole, typically prescribed at 600 mg per day, is also an alternative, but it demands careful examination of liver functioning due to the potential risk of hepatotoxicity; liver enzymes are recommended to be monitored every two weeks throughout the therapy, and the drug must be discontinued if significant hepatitis elevations or symptoms appear. Furthermore, oral itraconazole at 200 mg per day is also used; however, its ocular penetration is less effective than that of voriconazole. When administered orally at a dose of 200 mg per day, fluconazole exhibits high oral bioavailability and strong penetration into ocular tissue, making it particularly effective for treating deep-seated *Candida* infections. However, it is less efficient against filamentous fungal species. Intravenous miconazole (20–40 mg per kg daily) may be used in severe or refractory cases, often in combination therapy, though it is less common due to the availability of safer and more effective alternatives.[22,25]

New therapeutic strategies, such as intrastromal and intracameral antifungal injections, have emerged to enhance drug delivery in cases of deep or treatment-resistant fungal keratitis. Intrastromal injection of voriconazole (50 μg/0.1 mL) or amphotericin B (3–5 μg/0.1 mL) achieves sustained drug levels in the corneal stroma, offering improved efficacy in deep infections.[26] Several studies report high success rates, with repeated injections showing minimal complications; however, randomized trials provide mixed results, with some noting faster healing, while others report increased risks of hypopyon, corneal scarring, and perforation.[27] Similarly, intracameral injection delivers high antifungal concentrations directly into the anterior chamber in cases with severe stromal involvement or endothelial plaque formation. Amphotericin B (5–10 μg/0.1 mL) and voriconazole (50–100 μg/0.1 mL) are commonly used, with studies demonstrating good clinical outcomes and low complication rates.[28] Nevertheless, a randomized trial reported no significant improvement in healing or visual acuity over topical therapy and highlighted a higher incidence of cataract formation.[29]

4. Azole derivatives: mechanism of action and therapeutic potential

Azoles are characterized by their aromatic and electron-rich properties, consisting of a five-membered heterocyclic ring structure that includes a single nitrogen atom and at least one other atom besides carbon, such as nitrogen, oxygen, or sulfur.[30] Two main categories of azoles can be distinguished structurally: those with an imidazole nucleus and those with a triazole nucleus. Imidazole nucleus derivatives include fenticonazole, clotrimazole, econazole, tioconazole, ketoconazole, sulconazole, and miconazole; and triazole nucleus derivatives include voriconazole, itraconazole, fluconazole, and posaconazole.[1] Considering their significant biological activities against *Fusarium* spp., *Aspergillus* spp., and *Candida* spp., along with their broad spectrum of antifungal activity, azole derivatives have been utilized extensively for the management and treatment of progressive fungal infections.[6,31] Four distinct groups of azole antifungals have associations with structure–activity relationships (SAR). A heme-associating group without any substitutions serves as the critical ring for antifungal action. This three-atom spacer promotes the required length between the heme-associating group and the side chain. A halogen-substituted phenyl, which is essential to produce an inhibiting action, is a side chain within an azole derivative structure.

† MIC is defined as the lowest concentration of an antimicrobial agent (such as an antibiotic or antifungal) that visibly inhibits the growth of a microorganism after a specified incubation period.

In contrast, there is another side chain that can be optimized to enhance pharmacokinetic and pharmacodynamic characteristics.[32] Azoles possess the ability to fuse with other aromatic molecules (like benzene) because of the lipophilic basic nature of azoles with proton-accepting properties, to generate intricate scaffolds featuring distinct biological, chemical, and medicinal characteristics, such as benzimidazole, benzisothiazole, and benzotriazole.[33] The binding of the nitrogen atom (present in the fourth position in antifungal 1,2,4-triazoles and in the third position in imidazoles) with the heme of cytochrome P-450 prevents lanosterol demethylation, an essential stage in the synthesis of ergosterol. Azole compounds have two or three aromatic rings and typically contain halogen substitutions (fluorine in fluconazole, voriconazole, and posaconazole; whereas chlorine in ketoconazole, miconazole, and itraconazole). These halogen substitutions are essential for the antifungal properties, potency, and activity of azoles, and also contribute to their hydrophilicity; however, the lipophilic character is influenced by the number of aromatic rings. Except for fluconazole, the majority of azole antifungals have high lipophilicity, which makes them poorly soluble in an aqueous environment. Therefore, fluconazole exhibits minimal concentrations in ocular tissues.[6] But compared to the imidazoles, the family of triazole antifungal medications offered several benefits, including optimal solubility, a stronger affinity towards the targeted fungal enzyme compared to that of a human, and, consequently, exhibit superior selectivity and safety, as well as a wider spectrum of antifungal activity.[8]

4.1. Mechanism of action of antifungal azoles

Antifungal azoles share a common mechanism of action by targeting the enzyme lanosterol 14α-demethylase, which is essential for ergosterol synthesis in the fungal cell membrane. In contrast, polyene antibiotics directly bind to ergosterol in the fungal cell membrane, disrupting membrane integrity. Azoles work by disrupting the essential functions of ergosterol and substituting it with distinct, non-essential sterols.[8,34] Azoles interfere with the fungal cytochrome P450-dependent enzyme, lanosterol 14-α-demethylase (also known as CYP51p or ERG11p), which is responsible for converting lanosterol into 14-α-demethyl lanosterol in the ergosterol biosynthesis process, as demonstrated in Fig. 2.[35] Inhibiting the enzyme alters the levels of lanosterol, 14-α-demethyl lanosterol, and ergosterol, thereby modifying the permeability and flexibility of the fungal cell membrane. As a result, this will have an impact on the functioning of membrane-bound enzymes and impede the development and proliferation of fungal cells.[8,36] Azoles have also been proven to prevent the following desaturase phase in certain fungal species. Furthermore, azoles such as miconazole and voriconazole have

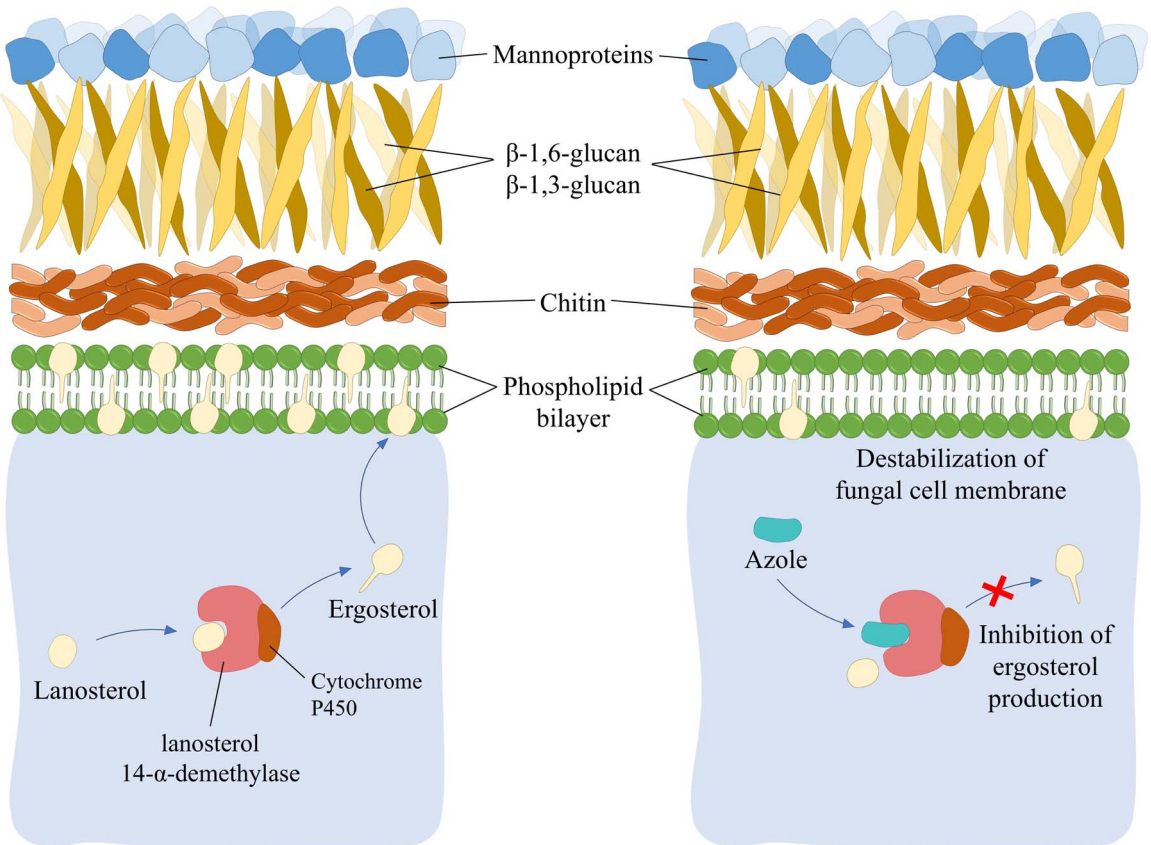

Fig. 2 Mechanism of action of azole antifungal compounds, demonstrating blocking of the conversion of lanosterol to ergosterol, an essential element of the fungal cell membrane.

shown promising fungicidal efficacy against Candida spp. Specifically, miconazole was found to be related to the production of reactive oxygen species (ROS) in biofilm cells.[37]

4.2. Promising azole derivatives for ocular antifungal therapy

The progression from experimental (preclinical) antifungal candidates to clinically approved ocular antifungal treatments has been slow owing to a multitude of complications. These encompass the anatomical and physiological restrictions imposed by the ocular barriers, the suboptimal physicochemical characteristics of drug candidates, and the non-selectivity of these drugs, which leads to toxicity. Furthermore, the progression of systemic and ophthalmic adverse effects, the increasing incidence of resistance and/or cross-resistance, and an insufficient *in vitro–in vivo* association of therapeutic efficiency impede this transition.[6] Notwithstanding these limitations, azole derivatives have recently attracted the attention of several researchers working to maximize the therapeutic effectiveness of these drugs by enhancing their antifungal

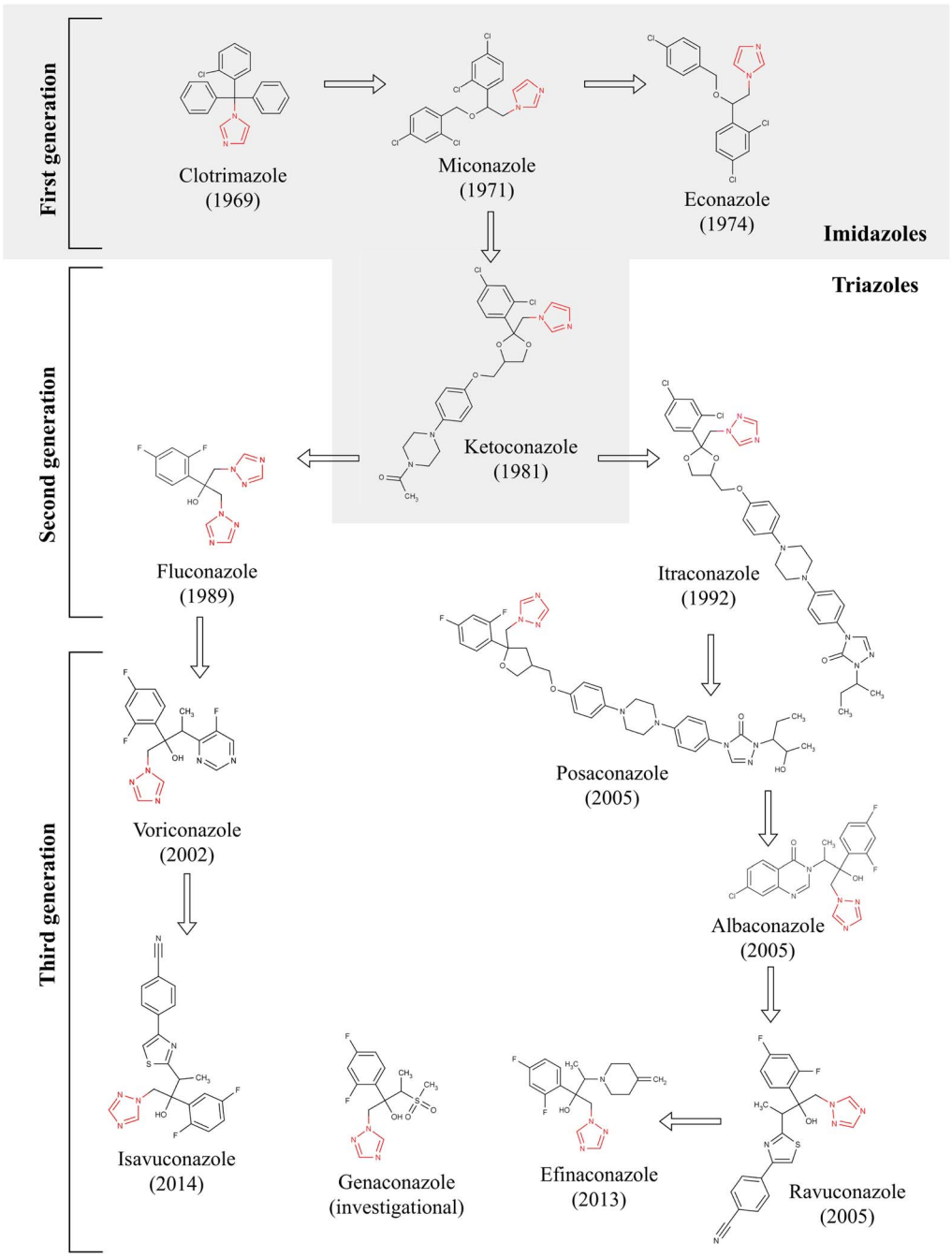

Fig. 3 Structural evolution of azole antifungal drugs, showing the transition from imidazoles to triazoles, with corresponding years of approval or development noted.

characteristics, reducing side effects, and ultimately improving patient outcomes. To achieve these goals, researchers are experimenting with various formulations and modifications, demonstrating that azole derivatives can serve as a crucial component in the treatment of ocular fungal diseases. Fig. 3 illustrates a comprehensive overview of the various azole antifungals that have been extensively researched for the treatment of ocular fungal infections.

4.2.1. Fluconazole. Fluconazole, a member of the triazole class of antifungal agents, was approved in 1989 due to its various advantages over previously available azole antifungal compounds, including better pharmacokinetics and a broad antifungal spectrum.[38] Fluconazole represents an effective option for treating profound *Candida* keratitis due to its safety and toxicity profile; however, it is not a recommended approach for treating filamentous fungal keratitis, as it has been demonstrated to exert weak-to-moderate effectiveness against the filamentous fungus but possesses superior effectiveness against *Candida* spp.[6,25] However, the drug has shown inadequate effectiveness against *Fusarium* spp. and *Aspergillus* spp.[8] Fluconazole exhibits substantial ocular penetration, achieving therapeutic concentrations through various delivery approaches, including topical and systemic administration. Due to its adaptability, it is a useful treatment for various ocular fungal diseases. Fluconazole is specifically effective against deep-seated mycoses that influence the posterior portion of the eye as well as superficial mycoses that affect the anterior segment. Because of its capacity to bypass across ocular tissues (barriers), it offers complete antifungal treatment and can effectively treat infections both in the front and the back of the eye. This broad-spectrum effectiveness highlights how useful it is for treating intricate ocular fungus infections.[3] Fluconazole differs from other azole antifungal derivatives in that it does not inhibit immunological cells, particularly lymphocytes. This attribute of azoles reduces the degree of tissue degradation caused by the inflammatory response, while also affecting the *in vivo* effectiveness of azoles, which is particularly lacking in the case of fluconazole.[39] Fluconazole ophthalmic formulation is available as Zocon® 0.3% w/v solution, providing an effective alternative for treating fungal keratitis and other ocular fungal infections.[40]

To produce more potent antifungal drugs, medicinal chemistry scientists have been working diligently on modifying the fluconazole structure and generating novel triazole derivative compounds. Substituting a single triazole ring of fluconazole with nitrotriazole and piperazine ethanol components resulted in sufficient antifungal properties against most fungal species (except *Aspergillus* spp.), while substituting with alkylated piperazine resulted in an optimal antifungal implication against *Candida* spp. (*C. albicans*, MIC = 0.016–0.98 μg mL^{-1}) and *Aspergillus* spp. (MIC = 0.05–0.97 μg mL^{-1}).[41,42] By substituting quinolone or coumarin substrates for fluconazole's triazole ring, a hybridization process may produce new and more effective antifungal compounds. Fluconazole derivatives containing benzotriazine moieties have shown an excellent antifungal effect against *Aspergillus* strains with MIC value of around 0.25 μg mL^{-1}.[33] Further, optimized antifungal activity of fluconazole derivatives against various *Candida* spp. (*C. albicans*, *C. krusei*, *C. glabrata*, *C. parapsilosis*, *etc.*) have been demonstrated by triazole ring replacement with piperazine–carbodithioate moiety, phosphonate moiety, oxadiazole moiety, indole moiety, benzofuran moiety, and pyrrolotriazine moiety.[43–46]

4.2.2. Voriconazole. Voriconazole was derived from fluconazole with the introduction of a methyl group to the propyl strand and replacement of one triazole ring with a 5-fluoropyrimidine group. This modification enhanced the binding affinity of the drug for lanosterol 14-α-demethylase and also increased its potential for inhibiting CYP51.[47] Voriconazole is a second-generation azole derivative of antifungal compounds, which received regulatory approval in 2002. The compound is effective in opposition to all fluconazole-resistant species of *Candida*, including *C. albicans*, *C. glabrata*, and *C. krusei*, as well as some *Aspergillus* spp. that are resistant to amphotericin B, such as *A. terreus*.[48] Due to its significant bioavailability (≈approximately 96 percent) and highly effective permeation across ocular tissues, voriconazole has emerged as a widely used oral formulation in the treatment of ocular fungal infections, particularly fungal keratitis. This has improved compliance among patients through developing a broad and potent spectrum of antifungal activity, and by maintaining optimal drug concentration levels in both the anterior and posterior parts of the eye.[3,49] However, systemic and intraocular (intrastromal, intracameral, and intravitreous) administration of voriconazole induces several side effects, including visual disturbances and increased light sensitivities in nearly 30 percent of clinical study participants. Additionally, various other toxic effects, including hepatotoxicity, have been documented when the drug is administered systemically *via* oral or intravenous routes, though in a limited number of cases.[39] The recommended dosages of voriconazole required to cause a half-degree reduction in ergosterol production (IC_{50}) in fungal isolates from *C. albicans* (2 μg L^{-1}) and *C. krusei* (20 μg L^{-1}) are much lower than the corresponding values for fluconazole (*i.e.*, around 10 and 230 μg L^{-1}, respectively). Among these two fungi, voriconazole is recognized as having more potent CYP51 inhibitory activity compared to fluconazole.[47,50] The drug has high potency against a wide spectrum of keratitis-causative fungi, including both *Fusarium* spp. (*F. solani*), *Aspergillus* spp. (*A. fumigatus*), as well as *Candida* spp. (*C. albicans*, *C. tropicalis*).[47] Due to the improved ocular penetrating characteristics and broad range of antifungal action of this new generation of azoles, they are being utilized extensively in the treatment of fungal keratitis.[51] Voriconazole, being a lipophilic compound with low aqueous solubility (0.061% at pH 7) and instability in aqueous environments, is encapsulated with a β-cyclodextrin derivative for IV use, which was first manufactured by Pfizer (Vfend®). This complex increases solubility and stability while maintaining lipophilicity and corneal permeability. The formulation containing 200 mg voriconazole is available as white lyophilized powder, which is prescribed to be reconstituted with water-for-injection (WFI) to formulate 20 mL of aqueous solution of 1% (10 mg mL^{-1} concentration) voriconazole, and this solution is administered as eye drops.[52,53] Similarly, Vozole Eye Drop

(Aurolob), another commercially available eye drop based on lyophilized powdered formulations, is specifically intended to aid in the management of ocular fungal infections. It is used as an independent remedy for treating keratitis caused by *S. apiospermum* and *C. albicans*.[29]

Researchers synthesized various structurally modified heterocyclic amines based on voriconazole, demonstrating improved antifungal activity against *A. fumigatus* and *C. albicans* with MIC_{80} values ranging from 0.015 to 0.126 μg mL^{-1}.[54] Moreover, the development of newer generation triazoly lbutanol-based voriconazole derivatives, such as isavuconazole, albaconazole, genaconazole, efinaconazole, and ravuconazole, involved strategic modifications to the fluoropyrimidine moiety on the side chain of the drug. While ravuconazole incorporates a thiazole ring and isavuconazole has a 2,5-difluoro analogue, albaconazole is made by replacing the fluoropyrimidine ring in voriconazole with the quinazolinone (pyrimidone-fused ring) functional group.[48,55,56] As a consequence, the novel class of broad-spectrum antifungal drugs known as triazolyl butanols, such as efinaconazole, albaconazole, ravuconazole, and isavuconazole, was identified and approved. Regarding a side chain fragment, different amines (alkylamino, cyclic amine) or heterocycles that possess nitrogen atom (thiazole, pyrrolidone, 1,2,3-triazole, tetrazole, imidazolidone, pyrimidone, triazolone, and triazinone) were more commonly employed.[48,57]

4.2.3. Ketoconazole. This lipophilic synthetic imidazole antifungal agent, prescribed for oral administration in two separate doses of 200 to 800 mg per day, is used to treat fungal infections of the eyes. Ketoconazole is effective against *Candida* along with other moulds, but has limited activity against the widely prevalent pathogenic filamentous fungus. However, the narrow spectrum of antifungal activity compared to other azole derivatives, and the hepatotoxicity of ketoconazole, which necessitates regular evaluation of liver health and function, are the two major limitations of this drug.[51,58] The US Food and Drug Administration (US-FDA) has indicated that the hepatotoxicity associated with ketoconazole arises from its extensive hepatic metabolism, primarily through oxidative *O*-dealkylation and aromatic hydroxylation pathways, which resulted in the discontinuation of ketoconazole tablets in many countries.[59] This drug was the first azole derivative to be approved for oral use by the US-FDA for the treatment of systemic fungal infection, outperforming earlier identified imidazole-based antifungals that were only effective in treating surface mycoses.

Furthermore, several adverse effects associated with the oral treatment of ketoconazole have been reported, including inadequate effectiveness and selectivity, as well as the recurrence of infection and oligospermia upon prolonged ketoconazole therapy *via* the oral route.[7,8] Ketoconazole, due to its potent inhibitory property against the CYP3A4 enzyme, has been found to have negative interactions with macrolide antibiotics, which are metabolized by this enzyme and alter the serum levels of the antibiotic. As such, elevated serum concentrations of these antibiotics may result in greater toxicity.[60] Also, owing to the higher molecular weight, hydrophobic properties, and protein binding characteristics of ketoconazole, the drug finds several limitations upon ocular administration because of its restricted ocular permeability rate across corneal tissues and BRB. Due to these drawbacks and the emergence of newer azole-based antifungal derivatives, fluconazole quickly replaced ketoconazole for the management of a variety of fungal infections. As a result, ketoconazole has limited efficacy in treating ocular fungal infections and is often used as an adjunct to other antifungal therapies.[50]

4.2.4. Itraconazole. Second-generation antifungal azoles, such as itraconazole, which have demonstrated an improved safety and toxicity profile, as well as a broader spectrum of antifungal action, resulted from substituting a triazole; however, potent inhibition of CYP3A4 persists as a limitation.[61] Itraconazole, a widely used antifungal agent, faces significant limitations due to its hydrophobic nature, characterized by a low water solubility of less than 5 μg mL^{-1} and a high protein-binding capacity. Approximately 90% of itraconazole binds to serum proteins, which severely restricts its ability to penetrate tissues effectively when administered orally. Systemic, oral (solutions or capsules), and topical (ointments and 1% ophthalmic solutions) forms of this medication are available, albeit not universally.[62] As new itraconazole analogues with a pyridine ring, Y. Liu *et al.* (2011) synthesized antifungal drugs that showed superior pharmacokinetic characteristics, substantially greater solubility, and bioavailability as compared to itraconazole.[63]

Additionally, the novel itraconazole derivative series developed showed a decreased LD_{50} and strong antifungal activity, as determined by 2- to 45-fold lower minimum inhibitory concentrations against several *Candida* spp. and *Aspergillus* spp. than itraconazole, along with negative genetic toxicity.[63] In another study, Y. Liu *et al.* (2013) developed analogues of itraconazole with amino acid ester prodrugs, such as proline, alanine, glycine, and valine, as well as phosphate prodrugs, including the phosphate disodium salt. These prodrugs exhibited a broad antifungal spectrum, covering Aspergillus spp. and *Candida* spp., and a good safety profile.[64]

4.2.5. Miconazole. Certain healthcare professionals in Ghana prescribe EPMD (extemporaneously prepared miconazole eye drops) to treat keratomycosis. L. Gyanfosu *et al.* (2017) determined the MIC of EPMD in their study using the agar-well diffusion technique. When in comparison with sterilized water, the MIC of EPMD against *C. albicans* was found to be 1.08 g of EPMD per 100 mL solution, yielding a zone of inhibition of 13 mm ± 0.578. However, no discernible change was reported in comparison to 0.3% fluconazole.[65,66] Miconazole exhibits strong antifungal action towards *Aspergillus* spp. but limited action against *Fusarium* species, as well as varying effectiveness against filamentous fungi.[2] However, miconazole, frequently used in conjunction with alternative antifungal agents, has demonstrated efficacy against certain uncontrolled fungal diseases. Research indicates that many *Scedosporium* apiospermum strains may remain susceptible to miconazole, regardless of whether they exhibit tolerance to conventional fluconazole and amphotericin B therapy.[67] The intravenous injection formulation can also be suitable for subconjunctival or 1% topical ophthalmic off-label application. Nonetheless, due to its large molecular weight, lipophilic nature, and protein binding,

miconazole has limited permeation across blood and corneal barriers.[2,68]

In a study performed by Kazeminejad *et al.* (2022), it was demonstrated that the 1,2,4-triazole compound, an analogue of miconazoles, possesses potential antifungal properties against five different fungal species. 3,4-Dichlorobenzyl analogue was found to be the most active. Additionally, compared to the nitrogen-substituted compound (nitrobenzyl), the antifungal property of 3,4-dichlorobenzyl derivative (MIC = 5 μg mL^{-1}), 2,4-difluorobenzyl analogue (MIC = 4 μg mL^{-1}), and 2-fluorobenzyl derivative (MIC = 16 μg mL^{-1}) could have been markedly enhanced by *Fluorine* or *Chlorine* substitution. Significantly, mono-substituted benzyl derivatives (MIC = 5 to 32 μg mL^{-1}) exhibited less efficacy as compared to substituted benzyl triazole compounds (MIC = 5 to 16 μg mL^{-1}).[69]

4.2.6. Posaconazole. For the management of chronic fungal keratitis caused by *Fusarium* species or *Fusarium* species that have developed resistant towards common azole derivatives (voriconazole, fluconazole, and ketoconazole), this second generation thiazole antifungal agent has proven to have promising effectiveness for the treatment of mycotic keratitis, either through oral therapy or in combination using a topically administered other antifungal formulations.[2] A. Altun *et al.* (2014) determined the antifungal potential of posaconazole for ocular fungal infections in their study, where the researchers demonstrated that resistant *Fusarium* keratitis can be managed by orally administered posaconazole with a dose of 200 mg QID‡ or 400 mg BID§ either by monotherapy or in combination therapy with topical ophthalmic dosage of 4–10 mg/0.1 mL.[70,71] According to a study performed by T. J. Ferguson *et al.* (2022), three patients with persistent fungal keratitis were successfully treated with high-dose orally administered posaconazole after conventional therapy failed. All three subjects responded quickly to high-dose therapy of posaconazole (500–600 mg daily), albeit one needed multiple treatments to address repeated episodes. All three cases reported previous histories of wearing contact lenses and infections that were confirmed by cell culture. A healthcare professional monitored the course of treatment, and no notable side effects were noted, demonstrating the efficacy of high-dose posaconazole in treating refractory patients.[51,72]

4.2.7. Alternative azole derivatives. Other azole-based therapies for ocular fungal infections may include clotrimazole, econazole, or isavuconazole. When preliminary treatment for fungal keratitis is contraindicated, isavuconazole may be implemented. It can be efficiently administered orally to treat fungal endophthalmitis caused by *Candida* spp. when the infection is improving. Although clotrimazole can be applied topically off-label (1%), in the form of eye drops or ointment, this drug does not appear to be the best option when taken as monotherapy. Lastly, econazole 1% is an ophthalmic medication that is effective against filamentous fungi, similar to natamycin. It received approval in the 1970s, but there is currently no evidence of its use as a main therapy for mycotic keratitis.[2]

4.3. Clinical translation of azole antifungals in ocular fungal disease treatment

Many research studies have been performed to thoroughly examine the therapeutic effectiveness of azole antifungals in treating various ocular fungal diseases. Optimizing the safety, effectiveness, and bioavailability of azole-based ocular therapies, either as monotherapy or in combination with other antifungal agents, has been a primary objective of these clinical translations. Prominent clinical studies are highlighted in Table 1, along with a summary of their conclusions and contributions to the treatment of these complex infections.

4.4. Molecular mechanisms of azole resistance in fungal pathogens

The resistance developed by various fungal species refers to their capability to withstand various antifungal drug dosages, which exhibit potent antifungal action against other susceptible strains. By determining the drug's MIC against a wide variety of antifungal strains, the threshold levels that differentiate resistant from susceptible strains can be established.[79] Resistance to azole antifungal derivatives can be induced by a variety of complex molecular processes, as illustrated in Fig. 4. One such molecular-level mechanism involves mutations in the CYP51A or *ERG11* gene, either *via* overexpression, gene amplification, or point mutation, which can lead to resistance as well as cross-resistance against all azole antifungal derivatives (Fig. 4D and E). This necessitates higher concentrations of azole antifungals due to the increased abundance of the target enzyme molecules, which are required to complex the entirety of the enzymes present within the cell.[80] The primary contributors of the overexpression of the *erg11* gene are either duplication of the complete chromosome-5 [i(5L)] *via* activating mutations in the gene responsible for encoding of transcription factor upc2 responsible for ergosterol biosynthesis, which further results in gene amplification, or the encoding of an isochromosome comprising two separate copies of the chromosomal left arm, where the *erg11* gene is present.[81,82]

Another primary mechanism conferring resistance to diverse antifungal agents involves point mutations in the gene encoding the target enzyme—specifically, *ERG11*/CYP51 in the case of azoles—resulting in amino acid substitutions that alter enzyme structure and reduce drug binding affinity (Fig. 4D).[82] Point mutations in *Aspergillus* spp. have been identified as single-point mutations in the CYP51A gene, resulting in amino acid alterations that affect the CYP51A protein. Such changes may alter the protein structure, stability, and functioning, making it more difficult to recognize substrates and ultimately resulting in unique characteristics of azole resistance.[79] Point mutations at glycine-54 (G54) and glycine-138 (G138) result in cross-resistance to itraconazole and posaconazole, whereas point

‡ An abbreviation derived from the Latin phrase *quater in die*, meaning "four times a day", which is commonly used in medical prescriptions to indicate that a medication should be taken four times daily at regular intervals.

§ An abbreviation derived from the Latin phrase *bis in die*, meaning "twice a day", which is commonly used in medical prescriptions to indicate that a medication should be taken two times daily.

Table 1 Summary of key clinical studies performed to evaluate the therapeutic effectiveness of azole derivatives for ocular fungal infections

Aim of the study	Interventions	Study outcome	References
Comparative therapeutic study of natamycin and voriconazole for fungal corneal ulcers (NCT number: NCT00557362)	Drug: natamycin 5% topical eye-drop, voriconazole 1% topical eye-drop Procedure: corneal de-epithelialization	Voriconazole and natamycin therapies for fungal keratitis did not significantly alter corneal perforations, scar size, or visual acuity, according to the research, which included 120 patients. A tendency towards poorer results was linked to scraping. Voriconazole was shown to slightly enhance BSCVA (best spectacle-corrected visual acuity); however, this difference was not considered statistically significant	73
To assess voriconazole and natamycin for fungal corneal ulcers	Drug: natamycin 5% topical, voriconazole 1% topical	Thirty patients participated in the trial, which evaluated two topical therapies for fungal corneal ulcers. Improvements in visual acuity and ulcer resolution time (24.3 days for voriconazole and 27.2 days for natamycin) were comparable for both regimens. The study finds no significant difference between the two therapies; both are effective and reliable	74
To compare the intrastromal voriconazole, amphotericin B, and natamycin as adjuncts to topical natamycin in treating recalcitrant fungal keratitis	Intrastromal-voriconazole 50 μg/0.1 mL, intrastromal-amphotericin B 5 μg/0.1 mL and intrastromal-natamycin 10 μg/0.1 mL	In comparison to intrastromal voriconazole (36.1 ± 4.8 days) and intrastromal amphotericin B (39.2 ± 7.2 days), intrastromal-natamycin therapy produced the most rapid healing (34 ± 5.2 days) with comparable healing success (90–95%). Although the intrastromal natamycin group required fewer repeated injections, the intrastromal amphotericin B group had a greater percentage of deep vascularization (55%)	75
To compare topical natamycin and voriconazole for treating filamentous fungal keratitis. (NCT number: NCT00996736)	Drug: 5% natamycin topical eye-drop, 1% voriconazole topical eye-drop	The study, involving 323 subjects, concluded that natamycin significantly improved visual acuity and reduced the need for keratoplasty or perforations, especially in cases of *Fusarium* infection. The results of the two therapies were comparable in non-*Fusarium* patients. In terms of clinical and microbiological results for smear-positive filamentous fungal keratitis, natamycin therapy succeeded over voriconazole	76
Comparing econazole and natamycin for managing fungal keratitis	Drug: 2% econazole topical eye-drop, 5% natamycin topical eye-drop	The investigation included 116 individuals with culture-positive fungal keratitis who were randomly assigned to receive treatment with either 2% econazole or 5% natamycin. There were no significant differences between the two therapies in terms of clinical conclusions, such as epithelial defect size, infiltrate size, or recovery duration. Both therapies were equally effective, with no variations in symptoms such as lid oedema, congestion, or hypopyon	77
Comparative study of natamycin and itraconazole topical therapy for fungal keratitis	Itraconazole 1% eyedrops, natamycin 5% eyedrops	Among 100 human participants having fungal keratitis, which is primarily caused by *Fusarium*, *Aspergillus*, and *Curvularia* spp., topical itraconazole therapy demonstrated positive outcomes, particularly in keratitis caused by *Curvularia* spp. (89% favorable reaction), but natamycin has shown higher effectiveness against *Fusarium* spp. (79% *vs.* 44%; $P < 0.02$). There were no notable side effects, and both treatments were well tolerated	78

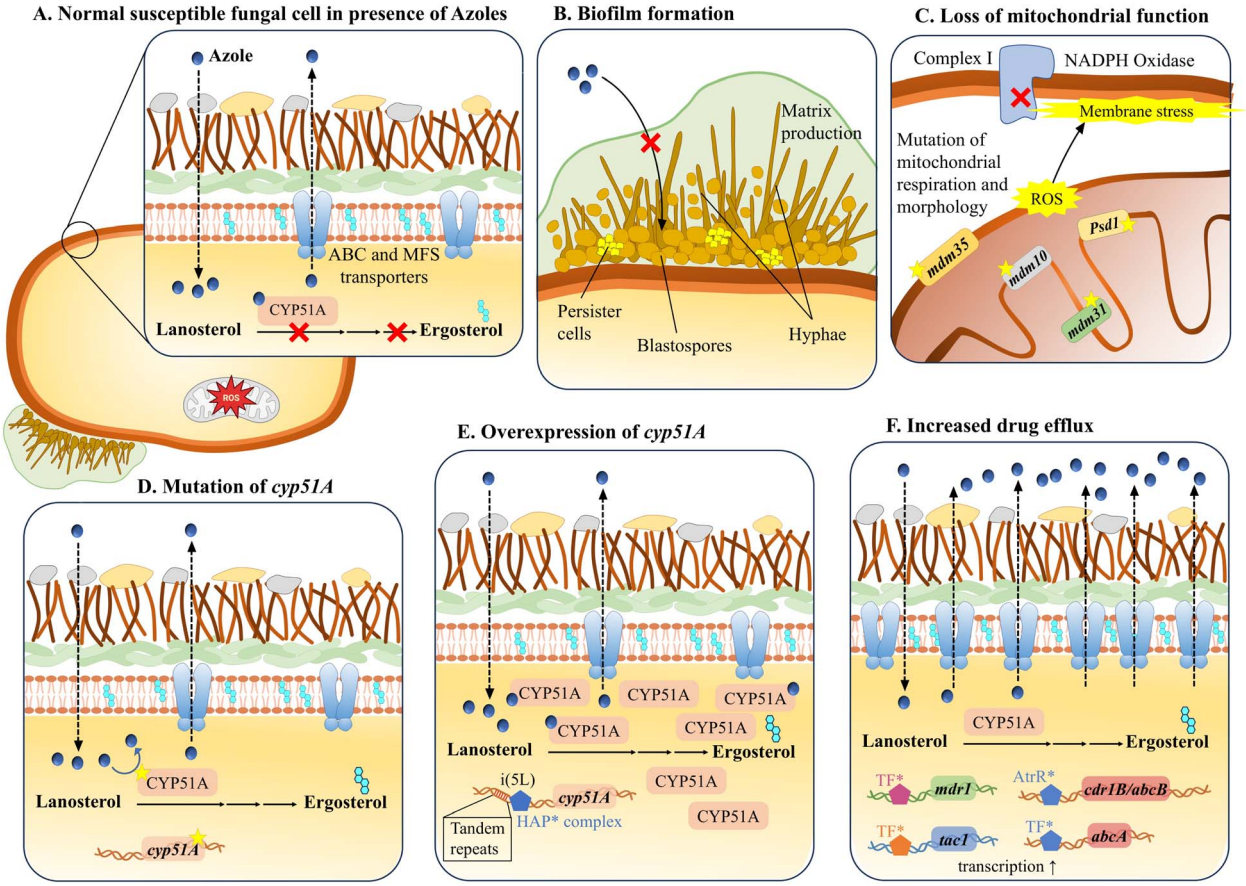

Fig. 4 Different molecular mechanisms of resistance to azole antifungals in fungal cells. (A) A fungal cell, demonstrating the fungal cell wall and cell membrane with various components, where sufficient intracellular concentrations of azoles inhibit *CYP51A*, which is required for the biosynthesis of membrane ergosterol from lanosterol, resulting in decreased amounts of ergosterol in the membrane. (B) Biofilm resistance is achieved by inhibiting the permeation of azole compounds into the fungal cell. (C) Inhibition of mitochondrial complex I results in azole resistance. (D) Mutations in *CYP51A* can reduce the binding affinity of azole compounds to their target, thereby inducing resistance. (E) Overexpression of *CYP51A*, mediated by the HAP complex, can lead to increased synthesis of the target enzyme, which in turn requires higher concentrations of azole antifungals to inhibit ergosterol biosynthesis, thereby contributing to azole resistance. (F) Increased drug efflux, due to overexpression of efflux pump proteins such as *cdr1*, *abcA*, *abcB*, *tac1*, and *mdr1*, can reduce the intracellular concentration of azole antifungals.

mutations at glycine-448 (G448) develop voriconazole resistance along with a reduced sensitivity against both itraconazole and posaconazole.[83,84] Furthermore, the substitution of an amino acid at methionine-220 (M220) has been linked to various occurrences of decreased triazole susceptibility.[85] Several other positions of point mutations reported includes, proline-216 (P216), substitution of phenylalanine-219 with cysteine (F219C) or isoleucine (F219I), alanine replaced by threonine at position 284 (A284T), tyrosine replaced by cysteine at position 431 (Y431C), glycine at position 432 and 434 substituted by serine (G432S) and cysteine (G434C), respectively. The combination of amino acid alterations along with tandem repeats in the promoter region; for example, tandem repeats of 34 base pairs along with substitution of leucine with histidine at position 98 (TR34/L98H), and tandem repeats of 46 base pairs along with substitution of tyrosine with phenylalanine at position 121 or threonine with alanine at position 289 (TR46/L121H/T289A); has also been linked to overexpression of *cyp51a*.[86] Clinical isolates of *A. flavus* were shown to be resistant against voriconazole, and alterations in the *cyp51c* gene T788G (threonine substitution with glycine at position 788) and Y319H (tyrosine substitution with histidine at position 319) have been linked to high voriconazole MIC.[87,88] In the case of *Candida* spp., point mutations in transcription factors result in the overexpression of Cdr1/Cdr2, Tac1, and Mdr1, which primarily encode facilitator efflux pumps. Several research investigations have found substitutions in amino acids that reduce fluconazole susceptibility against *Candida* spp. These modifications were mainly represented in the form of three "hot spot" locations within ERG11p. Molecular modelling of these amino acid substitutions showed that, when expressed in a susceptible background, consequently contributed to reduced fluconazole susceptibility indicating that these substitutions were highly organized either within the fungus-specific external loop, the anticipated catalytic location, or situated on the proximal surface, ultimately developing interactions with the loop or heme moiety on the active site.[82,89] Posaconazole is an example of a new-generation azole that retains its effectiveness against C.

albicans that have erg11 modifications, which render them resistant to previous azoles. Up to 5 mutations in the *erg11* gene are usually required to decrease posaconazole susceptibility due to their distinctive interactions with ERG11p.[90]

Increased efflux pump activity is another significant mechanism of azole resistance (Fig. 4F), where membrane-bound efflux pumps become activated, recognizing and expelling a wide range of chemical substrates, thereby conferring multidrug resistance. This results in the prevention of therapeutically efficient azole concentrations from accumulating within the fungal cells. This resistance develops through the overexpression of multidrug efflux pumps, primarily involving two types of transporter families: the major facilitator superfamily (MFS) and the ATP-binding cassette (ABC) superfamily.[80,82] ABC proteins are ATP-dependent transporters with a duplicated structure, comprising two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs) for ATP hydrolysis, which leads to the upregulation of CDR1 and CDR2 transporters. This mechanism mediates azole resistance by enhancing drug efflux and reducing the accumulation of the drug. In contrast, MFS transporters are proton anti-porters use multiple transmembrane segments (TMSs; which are the hydrophobic regions of a protein that span across the lipid bilayer of the cell membrane) and the proton-motive force, along with electrochemical potential, to drive drug substrate efflux.[91,92]

Additionally, the cellular stress-response system enables fungal cells to survive azole-induced membrane stress, providing both basal tolerance and acquired resistance through various mechanisms. Because azole derivatives stimulate increased ROS production, the inhibition of the mitochondrial complex I in *Aspergillus* spp. is an area of interest in terms of azole resistance in the fungal cells (Fig. 4C).[93] By establishing stability in a large number of substrate proteins important for modulating the cellular signaling cascade, heat shock protein 90 (HSP90) monitors the intricate cellular circuitry within a fungal cell. *Candida* spp. tolerance against azole derivatives is decreased, and the development of azole resistance can be prevented when HSP90 is inhibited. Instead, azoles are more effective against resistant *Candida* spp. when drugs inhibiting HSP90 are used in combination.[94]

Another mechanism by which resistance to azole antifungal drugs develops is biofilm formation (Fig. 4B), in which a coordinated and organized microbial population adheres to a surface and becomes enclosed inside an extracellular matrix that the fungal organism produces on itself, thereby preventing the antifungal drugs from invading.[95] However, a few types of antimycotic drugs have demonstrated effectiveness over fungal biofilms, including liposome-based formulations of amphotericin B (polyenes), echinocandins, and miconazole (azoles).[37,96]

5. Challenges in azole-based ocular pharmacotherapy

Azole-based pharmacotherapy for ocular fungal infections faces several significant challenges, among which managing toxicity is a critical concern. Systemic voriconazole treatment for an extended period of time has already been linked to skin-related malignancies, such as squamous-cell carcinoma and melanoma, as well as phototoxicity. Systemic complications and toxicities are an important consideration when delivering azole antifungal drugs either orally or intravenously for the treatment of ocular fungal infections. These complications may include hepatotoxicity induced by ketoconazole, fluconazole, and voriconazole, as well as gastrointestinal problems associated with itraconazole.[97,98] In addition to systemic voriconazole treatment, topically administered voriconazole has previously been shown to cause dysplastic alterations on the surface of the eye.[99] M. Palamar *et al.* (2015) first published a case of ocular surface dysplasia in a 73 year-old male patient, who had been on topical 1% voriconazole for four months to treat graft-related fungal endophthalmitis caused by *Candida* spp. The patient then developed a yellowish, viscous lesion on the corneal surface that originated from the nasal limbus.[100]

Furthermore, the effective delivery of drugs to the targeted ocular sites, whether on the surface or within the intraocular tissues, is hindered by the complex anatomy of the eye. The ocular anatomy is divided into two distinct components based on the eye lens, namely, the anterior segment (includes the cornea, conjunctiva, iris, ciliary body, aqueous humor, and lens) and the posterior segment (consists of the sclera, choroid, retina, and vitreous body). Each of these segments plays a crucial role in the overall function and health of the eye and is susceptible to different types of ocular fungal infections. The primary disadvantage of topical drug administration is the challenge of effectively distributing the drug to various ocular tissues, largely due to the presence of multiple ocular barriers.[6,101] The ocular barriers are broadly classified into two categories: static barriers and dynamic barriers. These barriers serve as the primary defense mechanisms, meticulously regulating and preventing the entry of foreign substances—including therapeutic agents—from infiltrating and targeting the various tissues within the eye. Cornea, conjunctiva, sclera, vitreous humor, blood aqueous barriers (BAB), and blood retinal barriers (BRB) constitute the ocular static barriers, whereas tear film, tear turnover, nasolacrimal duct drainage, conjunctival and choroidal blood flow, and lymphatic clearance are the main components of the dynamic barriers. These ocular barriers significantly reduce the ophthalmic bioavailability of numerous drugs by blocking the passive absorption of various pharmaceutical compounds. The intricate anatomy of the human eye, highlighting various barriers that impede the absorption of topically administered drugs, is demonstrated in Fig. 5.[101–104] The corneal epithelium is a lipophilic and tightly packed layer, which presents a significant barrier to the permeation of hydrophilic and higher molecular weight compounds. Azoles, due to their lipophilic nature, may exhibit limited penetration across the hydrophilic stroma. Although more permeable than the cornea, the conjunctiva and sclera restrict the penetration of larger or lipophilic compounds, primarily facilitating systemic absorption rather than targeted intraocular delivery, resulting in significant drug loss. Further, the BAB, which consists of non-pigmented ciliary epithelium and the endothelium of iris vessels, and the BRB, which consists of tight junctions in the

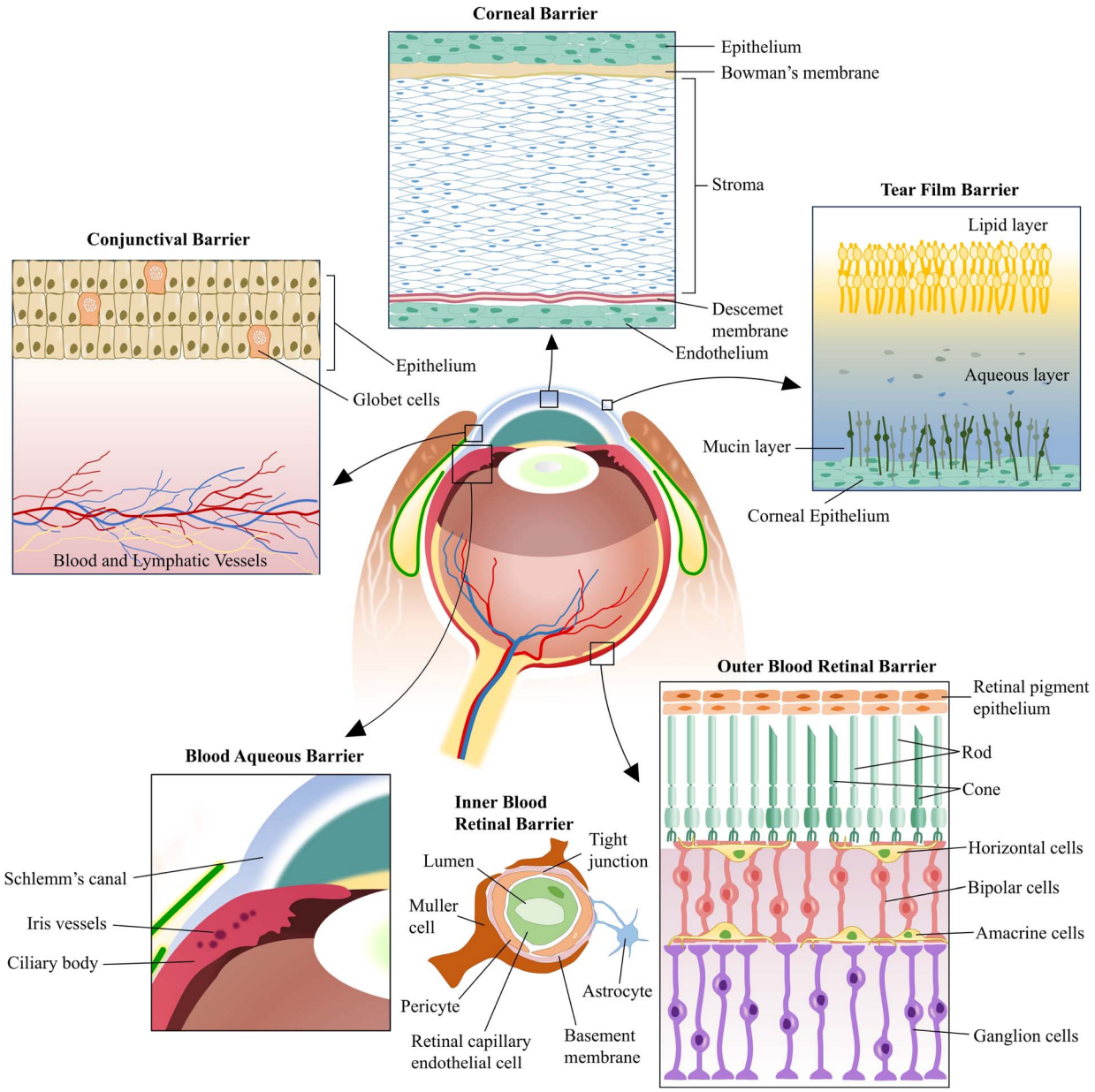

Fig. 5 Various ocular barriers that impede efficient drug delivery to targeted ocular tissues, highlighting both static and dynamic obstacles, including the tear film barrier, corneal epithelium, conjunctival barrier, BAB, and BRB.

retinal capillary endothelium and the retinal pigment epithelium, significantly restrict the entry of systemically administered azole drugs into aqueous and vitreous humor, thereby limiting their therapeutic efficacy in the treatment of ocular infections. The highly vascularized conjunctival and choroidal circulatory systems in the eye lead to systemic absorption of topically administered drugs from the ocular surface, resulting in low ocular bioavailability.[105]

The physicochemical properties of azole antifungals, such as molecular weight and aqueous solubility, significantly impact their absorption and penetration across ocular barriers, influencing their ability to target the infected site within the ocular environment. Lipophilic agents, including itraconazole, readily traverse the BAB and the lipid-containing membranes composed of epithelial and endothelial cells. However, the drug's interaction with proteins (like albumin) and enzymes found in the tear-lipid film, as well as its high molecular weight and lipophilicity, limit its corneal penetration when applied topically. On the other hand, hydrophilic drugs may easily navigate across the corneal stroma, while biphasic molecules with both lipid and aqueous solubility cross all corneal layers. It is difficult for compounds having a molecular mass greater than 500 Da to pass through the corneal epithelial layer. Due to their higher molecular mass, lipophilic properties, and high protein affinity, ketoconazole (531.45 Da) has also demonstrated limited penetration through the corneal and blood-ocular barriers. Miconazole (416.11 Da) and fluconazole (306.31 Da) are examples of compounds with intermediate molecular

weights, whose ocular penetration is likely influenced by both molecular mass and lipid solubility.[6,10,106]

When treating ocular fungal infections with monotherapy, the selective action of different azole antifungals also poses severe challenges. Numerous pathogenic fungus species, each with varying susceptibilities to azole antifungal treatments, frequently cause these illnesses; therefore, using a single azole antifungal may be insufficient to completely eradicate the infection.[6] Corneal fungal infections, such as fungal keratitis, are generally caused by filamentous fungi or moulds (for example, *Aspergillus* spp., *Fusarium* spp., *Curvularia* spp., and *Paecilomyces* spp.), as well as yeast or yeast-like fungi (for example, *Candida* spp., *Cryptococcus* spp.).[22] Topically administered ophthalmic therapy using natamycin, which possesses selective and potent effectiveness against filamentous *Aspergillus* and *Fusarium* spp. however, only weak to moderate action against *Candida* spp. has been adopted as the primary first-line therapy for managing superficial ocular infections caused by *Fusarium* and *Aspergillus* spp. However, natamycin monotherapy does not produce efficient effects in fungal keratitis, where filamentous fungi as well as yeast-like fungal pathogens are involved. As a result, an off-label multidrug regimen consisting of natamycin and azole antifungal drugs, such as miconazole, itraconazole, ketoconazole, or fluconazole, was started.[21,107]

6. Innovative formulation approaches for azole delivery in ocular antifungal therapy

As previously discussed, the primary drawback with topical drug administration for ocular delivery of a drug is that several physiological and anatomical barriers cause a substantial loss of delivered medication, meaning that only minimal concentrations of the drug reach the targeted ocular tissues. Drugs applied topically can reach the intraocular regions *via* two routes: the corneal pathway (through the cornea, aqueous humor, lens, and vitreous humor) or the conjunctival-scleral pathway (*via* conjunctiva, sclera, and choroid), as shown in Fig. 6. Topical administration is the first-choice, most common, and straightforward approach for ocular drug delivery in the management of various ophthalmic diseases, owing to its advantages, including non-invasiveness, minimized systemic side effects, and relative ease of patient self-administration.[108,109] However, the primary disadvantage of the topical route for ocular drug delivery is its extremely low bioavailability, typically less than 5% and to maintain the optimum level of drug concentration within ocular tissues, repeated installations of medication are prescribed, which ultimately result in poor patient compliance and potential adverse effects.[102] Apart from the topical route, several other ocular drug delivery approaches are available, each designed for site-specific medication delivery within the eye to enhance therapeutic efficacy. Examples include intracameral injections, which target the anterior segment of the eye; subconjunctival administration, an effective route for delivering drugs to the anterior or posterior ocular segments by injecting the medication beneath the conjunctiva bypassing the corneal and blood-aqueous barriers; intravitreal administration, which involves direct injection of drugs into the vitreous humor to target the posterior ocular tissues; retrobulbar administration, where the medication is targeted behind the eyeball in the retrobulbar space by injecting needle through the eyelid and orbital fascia; peribulbar administration, which

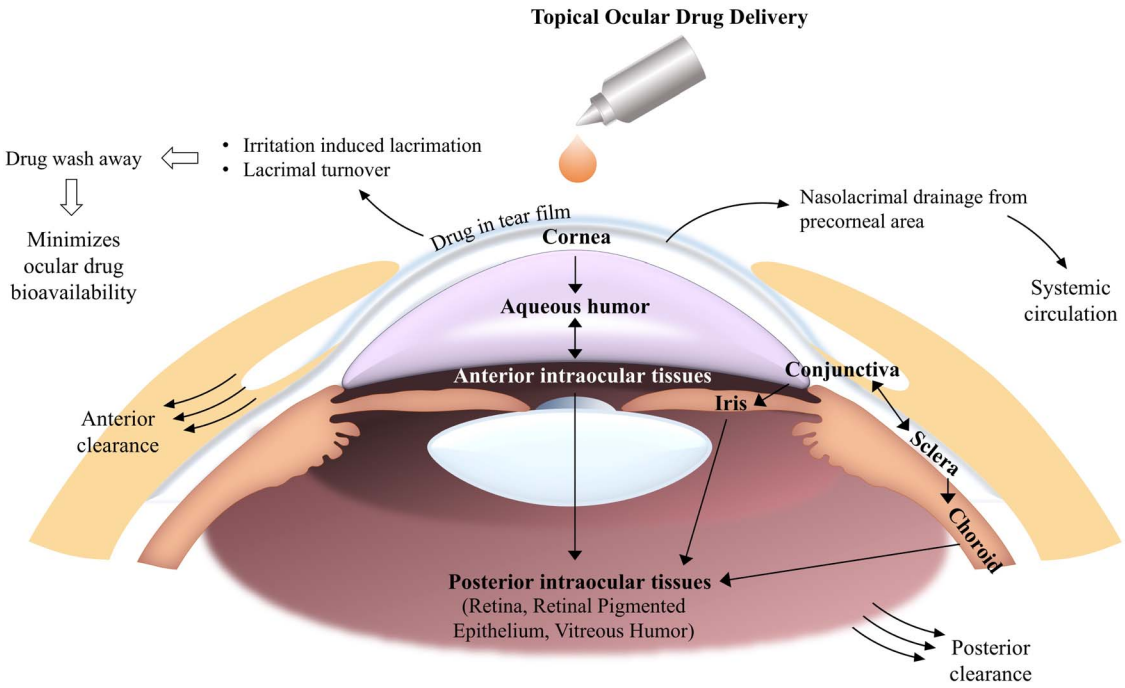

Fig. 6 Drug distribution pathways following topical ocular administration, highlighting the corneal and conjunctival/scleral routes of drug penetration.

involves injecting the drug into the orbital fat around the muscles of the extraocular region in the inferior lateral quadrant, *etc.*[110–113] Because of the invasive implications of these procedures and other potential challenges, these approaches require trained medical professionals. Topical administration is the only method of ocular drug delivery that patients can effectively self-administer without requiring assistance from medical professionals.[114,115] However, there is a vital requirement to improve the potency and efficacy of the topical route for ocular drug delivery. In contrast, researchers are increasingly focusing on the development of innovative nano-based drug delivery approaches. These advanced approaches seek to address associated limitations, improve bioavailability, and precisely target the intended intraocular tissues.[116,117]

6.1. Nano-systems designed for ocular drug delivery

Ocular drug delivery nanosystems have been developed to address complications caused by the intricate ocular structure, which makes it difficult for drugs administered *via* conventional topical ophthalmic formulations to be absorbed and retained effectively (Fig. 7). These nanosystems enhance drug permeation, extend residence duration, and enable targeted delivery, greatly increasing ocular bioavailability and therapeutic effectiveness. Nanosystems have considerable potential for managing various ocular fungal infections by preventing the degradation of medicinal agents and enabling controlled release, which would ultimately improve patient outcomes and reduce the need for repeated applications.

6.1.1. Polymeric nanoparticles. Polymeric nanoparticles with a size range of less than 400 nm provide an advantage in the efficient topical transportation of large, weakly aqueous-soluble compounds across various anatomical barriers of the eye.[118] Because the outer layer of the corneal and conjunctival surface is negatively charged, electrostatic attraction can draw positively charged nanoparticles to these tissues. As a result, topical medication distribution throughout the anterior ocular area is accomplished, and positively charged nanoparticles are retained on anionic eye tissues.[119] The physicochemical attributes of nanoparticles play a decisive role in determining their ocular biodistribution and overall therapeutic potential. B. Mahaling *et al.* (2016)[120] demonstrated that particle size, maintained below 250 nm across all formulations, facilitated permeation through ocular barriers while avoiding aggregation, thereby ensuring consistent dispersion and surface interaction. Surface charge emerged as a decisive factor: chitosan-coated nanoparticles with positive zeta potentials (+35 to +45 mV) exhibited enhanced bioavailability in the conjunctiva, sclera, choroid, and retina due to strong electrostatic interactions with

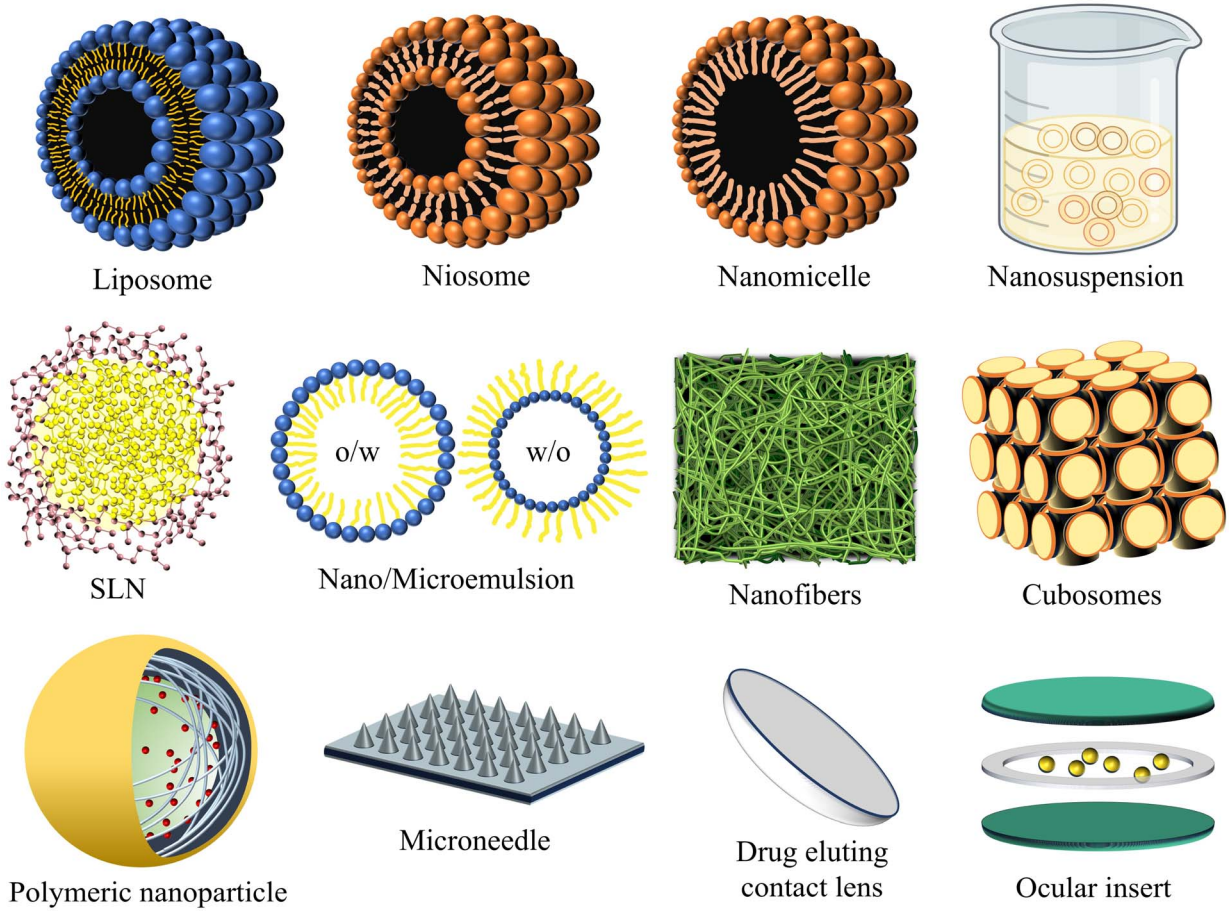

Fig. 7 Diagrammatic representation of various nanoformulations utilized in ocular drug delivery systems for enhanced therapeutic efficacy.

negatively charged mucins and their ability to transiently open epithelial tight junctions.

In contrast, negatively charged formulations, such as Pluronic F68-coated nanoparticles (−40 mV), while more stable, demonstrated relatively reduced retention and permeation. Hydrophilicity further influenced distribution pathways, as all nanoparticles with hydrophilic exteriors predominantly utilized the conjunctival-scleral route. Findings showed that mucoadhesive coatings, particularly PF68 and chitosan, prolonged residence at the ocular surface and enhanced tissue penetration, thereby improving spatiotemporal biodistribution compared with uncoated controls. Importantly, shell composition exerted greater influence than core type, underscoring the critical role of surface properties in mediating tissue-specific internalization, permeability, and retention.[120] Polymeric nanoparticles can deliver high drug payloads due to their broader surface-to-volume ratio, and their hydrodynamic dimension also optimizes pharmacokinetic characteristics.[121] Several polymers, including chitosan, poly(ε-caprolactone), carbopol, alginate, hyaluronic acid, eudragit, poly-(butyl) cyanoacrylate, and poly(lactic-*co*-glycolic acid), were recently utilized to formulate polymeric nanoparticles for an efficient delivery of drugs through the topical ocular route. Drug-incorporated polymeric nanoparticles may take the form of nanospheres or nanocapsules. For nanocapsules, the therapeutic compound is confined inside the polymeric envelope, and for nanospheres, the therapeutic compound is distributed within the matrix component.[121,122] A. M. Almehmady *et al.* (2022) developed an optimized formulation of fluconazole-loaded polymeric nanoparticles utilizing PEGylated poly(ε-caprolactone) through a solvent evaporation method. The morphological characterization of the optimized formulation revealed spherical polymeric nanoparticles with a particle size of approximately 200 nm, which is ideal for permeating various ocular membranes. Additionally, the developed formulation exhibited significant antifungal activity against standard *C. albicans* strains.[123]

6.1.2. Solid lipid nanoparticles (SLNs). SLNs, which range in size from 10 nm to 500 nm, are colloidal nanocarrier assemblies composed of lipid components dispersed in an aqueous surfactant solution. SLNs are particularly suitable for delivering both hydrophilic and hydrophobic drugs. They have demonstrated enhanced retinal permeation and the ability to provide sustained drug release over an extended period at the ocular site. Furthermore, SLNs can potentially minimize toxicity associated with the frequent administration of high drug doses. Triglycerides, like tristearin (Dynasan 118), tripalmitin (Dynasan 116), and trimyristin (Dynasan 114), a combination of monoglycerides, diglycerides, and triglycerides, like glyceryl behenate (Compritol 888 ATO), glyceryl palmitostearate (Precirol ATO 5), waxes (beeswax, carnauba wax), fatty acids (lauric, stearic, and myristic acid), and the corresponding fatty alcohols are the most commonly used solid lipids for the development of SLNs.[119,124]

L. Zhen *et al.* (2021) developed econazole-loaded SLNs as eye drops to address the poor solubility and ocular irritation associated with econazole. The drug, incorporated into SLNs prepared using a microemulsion method, exhibited a uniform spherical morphology with an average particle size of 19 nm and good stability. Compared with an econazole suspension, the SLNs showed controlled release, significantly higher corneal permeability, and enhanced antifungal activity against *Fusarium* spp. without causing ocular irritation. *In vivo* pharmacokinetic analysis performed on rabbits revealed improved ocular bioavailability, with corneal drug concentrations maintained above the MIC for 3 hours following a single administration, supporting their potential as an effective therapy for fungal keratitis and other ocular infections.[125]

The development of dual SLNs is another advantageous SLN-based delivery method used in ocular therapies, as demonstrated by Carbone *et al.* (2020). The study involved the development of SLNs for the dual delivery of clotrimazole (CLZ) and alpha-lipoic acid (ALA) to enhance antifungal efficacy against *C. albicans* mycosis. The SLNs, prepared with varying surface charges, were characterized physicochemically and biologically, demonstrating potential for synergistic topical antifungal therapy. Both drugs were efficiently encapsulated, with entrapment efficiencies of 77.86% (CLZ) and 80.63% (ALA). The *in vitro* release profile of both drugs from the co-incorporated SLNs has provided a controlled release rate, whereas CLZ and ALA as free drugs demonstrated a burst diffusion. The findings indicated that the developed CLZ–ALA-loaded SLNs exhibited high homogeneity, decreased average particle sizes, and good physical stability, as confirmed by samples stored at 25 °C for 15 days.[126]

6.1.3. Liposomes. Liposomes have recently been widely explored as potential topical ocular delivery nanosystems due to their biodegradability, biocompatibility, and capability to transport both hydrophilic and lipophilic drugs. The lipid bilayer membrane of these spherical vesicles encapsulates hydrophobic agents within its structure, while hydrophilic compounds are dispersed in the aqueous core.[127] Liposomes effectively penetrate drugs across ocular tissues through interacting with the surface of the cornea and conjunctiva, which is particularly significant for large molecular size, weakly soluble, or lower dispersion coefficient compounds. Liposomes deliver the encapsulated active compounds by interacting with ocular cells through various mechanisms of drug entry. These include endocytosis, specific or nonspecific adsorption on the cell surface, fusion with the cell membrane, and lipid exchange mediated by transfer proteins.[128] M. A. Moustafa *et al.* (2017) developed a fluconazole-incorporated hyaluronic acid-integrated liposomal formulation that leverages the synergistic properties of hyaluronic acid and liposomes to create an innovative ocular drug delivery system for the management of fungal keratitis. Unlike classical liposomes, which are solely phospholipid-based vesicles encapsulating the drug, this formulation incorporates liposomes within a hyaluronic acid-based hydrogel matrix known as hyalugel. This combination provides several distinctive benefits: the hyalugel acts as a viscous, bioadhesive scaffold that significantly enhances the retention time of the liposomal vesicles on the ocular surface by resisting rapid tear drainage. Furthermore, the gel matrix preserves the structural integrity of the liposomes, preventing

their rapid disintegration, which is a common limitation in conventional liposomal systems due to their fluid nature. The presence of hyaluronic acid also improves mucoadhesion and hydration, mimicking the natural tear film and enhancing patient comfort. Numerous advantages were provided by this system, such as increased permeation, controlled drug release, prolonged antifungal action, and an elevated structural integrity due to the gel-based formulation. It also overcomes the fluid character of liposomes, resulting in rapid drainage from the eye.[129]

6.1.4. Niosomes. These vesicular nano-systems offer an enhanced method of delivering integrated drugs, ensuring a longer retention time in intraocular tissues while decreasing systemic drainage, thereby lowering systemic toxicity.[130] These lipid-based, self-assembling, non-ionic carrier systems increase intraocular bioavailability by releasing the incorporated compounds irrespective of pH, and they also efficiently bind to the corneal surface. They exhibit similar characteristics to those of liposomes with high chemical stability, are non-toxic, non-immunogenic, biodegradable, and biocompatible.[131] Although niosomes and liposomes have structural and functional similarities, niosomes are made of non-ionic amphiphilic molecules dissolved in aqueous solutions rather than phospholipids through a self-assembling method, which makes niosomes more resistant to degradation by oxidation as compared to liposomes because they lack phospholipids.[132] Following their minimal toxicity, penetration-enhancing characteristics, improved physical stability, and targeted dispersion at the specific ocular site, niosomes have been studied as a possible ophthalmic drug delivery system.[133] In a research study performed by O. A. E. Soliman *et al.* (2017), the niosomal gel-based formulation incorporating fluconazole was developed to enhance ocular bioavailability through sustained drug release. Unlike conventional niosomes, which are vesicular systems composed of non-ionic surfactant bilayers dispersed in an aqueous medium, the niosomal gel formulation integrates these vesicles into a semi-solid gel matrix. This gel incorporation offers distinct advantages over conventional niosomes: the gel matrix increases the viscosity of the formulation, thereby improving its residence time on the ocular surface by reducing rapid drainage from the eye. Additionally, the gel provides a more stable environment for the niosomes, helping maintain the integrity and size distribution of the vesicles during storage and application. The niosomal formulation was optimized and characterized in terms of particle size, zeta potential, entrapment efficiency, and drug release patterns. Furthermore, the niosomal gel demonstrated better bioavailability in the targeted rabbit ocular tissues, and the pharmacokinetic investigation revealed increased drug retention and potential for therapeutic use.[134] Overall, niosomal formulation displayed improved stability and bioadhesive characteristics, making it an attractive alternative for ocular drug administration.

6.1.5. Nanomicelles. Nanomicelles are self-assembling nanoscale colloidal dispersions, typically ranging from 5 to 100 nm in size. These structures feature a hydrophobic core and a hydrophilic shell, formed by amphiphilic molecules that self-assemble into spherical or cylindrical nanoparticles in aqueous environments. The hydrophobic tails congregate within the core, while the hydrophilic heads interact with the surrounding aqueous medium.[132] The hydrophilic stroma, comprising 85–90% of the cornea, serves as a rate-limiting barrier for the ocular topical delivery of hydrophobic drugs. Nanomicelles are useful for formulating hydrophobic drugs that are incorporated into the micelle core, enabling the administration of a transparent aqueous solution into the conjunctival sac, thereby eliminating the sticky experience and obscured vision commonly associated with ocular application of ointments. The potential of nanomicelles to increase contact time with the eye's surface and minimize drug clearance *via* tear drainage or eye blinking becomes an additional crucial characteristic, which can be achieved through mucoadhesion or by making the formulation more viscous. Furthermore, nanomicelles have been demonstrated to effectively reach the posterior ocular tissues, primarily *via* the conjunctival-scleral route.[135–137] B. Wu *et al.* (2022) incorporated voriconazole in the core of mixed nanomicelles, which was developed using 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[maleimide(polyethyleneglycol)-2000], phospholipid (PL), and Pluronic F127. The micellar formulation aimed to manage fungal keratitis by prolonging precorneal retention through the bioadhesion of maleimide to the ocular mucosa.[138]

6.1.6. Microemulsion and nanoemulsion. Transparent, kinetically stable dispersion systems comprising two immiscible liquids, typically water and oil, with droplet sizes ranging from 50 to 500 nm, are known as nanoemulsions. However, they are thermodynamically unstable and can be stabilized utilizing amphiphilic surfactants, which consist of an exterior phase (continuous dispersion medium) and an interior phase (dispersed droplets). The size range of the droplets and physical stability properties of nanoemulsions enable them to be differentiated from microemulsions. Microemulsions are transparent, isotropic systems of sphere-shaped droplets of either the aqueous or oil phase, with droplet size ranging from 10 to 200 nm, distributed in an external oil or aqueous phase, respectively.[139] Although nanoemulsions and microemulsions have identical formulation constituents—comprising oil and aqueous phases, surfactants, and occasionally cosurfactants—their composition ratios vary, since microemulsions involve a comparatively higher surfactant-to-oil ratio.[132] Among the different forms of nanoemulsions, such as oil-in-water (o/w), water-in-oil (w/o), and bi-continuous nanoemulsions, the o/w type has become increasingly prominent in ocular pharmaceutical delivery because of its distinct advantages, which include the ability to incorporate hydrophobic drugs in the oil component and the simplicity of dilution in tear fluids.[132,140] Surfactants improve drug permeability and penetration through the corneal barrier in both microemulsions and nanoemulsions. Microemulsions ensure effective distribution over the surface of the eye and optimal dilution with tear fluid.[141] Z. Sehrish *et al.* (2024) developed three biocompatible microemulsion formulations containing the antihypertensive drug brinzolamide (BZD) for topical ocular use. The formulations were optimized with specific ratios of isopropyl myristate (oil), water, 2-propanol (co-surfactant), and different surfactants

(Tween 80, Tween 20, and Tween 60). Phase diagrams and microscopy confirmed the optimal composition and drug loading of each formulation (1–2% BZD). The FTIR analysis demonstrated the successful encapsulation of BZD without any chemical interactions. *In vitro* drug release studies demonstrated enhanced and sustained delivery of over 99% of BZD within 10 hours, indicating these microemulsions are promising candidates for effective ocular drug administration.[142] Utilizing the spontaneous emulsification technique, S. Mehrandish *et al.* (2021) developed an optimal nanoemulsion formulation containing itraconazole to enhance ocular administration and accomplish a prolonged drug release. The resultant two optimized nanoemulsion formulations, as determined by the pseudo-ternary phase diagram and DOE, exhibited appropriate globular sizes of 223.5 ± 10.7 nm and 157.5 ± 14.2 nm, and both appeared thermodynamically stable. In addition to their longer retention duration on the outermost ocular surface, formulations with an extended-release profile that increases by approximately 7-fold in 60 hours may result in higher intraocular bioavailability.[143]

Another type of colloidal drug delivery system is the self-nanoemulsifying drug delivery system (SNEDDS), which consists of an anhydrous mixture of oil, surfactants, and co-surfactants that, when combined with an aqueous solution, forms an emulsion. The interaction with aqueous media helps achieve enhanced ocular bioavailability of lipophilic drug compounds. B. N. V. Rasoanirina *et al.* (2020) incorporated lipophilic voriconazole into SNEDDS, which demonstrated improved permeation across the corneal barrier, with a permeability coefficient of ($1.98 \pm 0.184 \times 10^{-6}$ cm s^{-1}). The researchers used isopropyl myristate as the oil phase, PEG 400 as the co-solvent, Tween 80 as the surfactant, and Span 80 as the co-surfactant for the optimal SNEDDS formulation.[144]

6.1.7. Nanosuspension. Nanosuspensions provide an innovative approach to deliver larger amounts of weakly soluble medicinal compounds and longer retention time to the intended location within the cul-de-sac. These colloidal biphasic dispersed nanosystems overcome the limitations associated with conventional ocular suspension formulations, such as poor intrinsic solubility and saturation solubility in lachrymal fluids, low ocular bioavailability, and irritation due to the large particle size.[145] In research performed by P. Pawar *et al.* (2021), the potential of Eudragit RS-100-based nanosuspensions was explored to enhance the intraocular delivery of itraconazole, using a solvent evaporation technique. The optimized formulation possessed particle sizes ranging from 332.5 nm to 779.3 nm, along with a zeta potential of +0.609–16.5 mV, and an entrapment efficiency of 61.35–76.35%. *Ex vivo* corneal penetration examinations demonstrated better drug penetration than commercial itraconazole ophthalmic drop formulations, while further characterization confirmed the long-term stability and compatibility. Furthermore, antifungal assessment showed increased effectiveness against *A. flavus* and *C. albicans* spp.[146]

6.1.8. Nanofibers. With a size range of less than 1000 nm, these one-dimensional nanosystems are characterized by their filamentous morphology. Due to their low fabrication costs, versatility in employing a variety of polymers, simplicity of synthesis through various procedures, significant porosities, large surface areas, controllable mechanical characteristics, and variable morphologies, nanofibers have recently found applications in drug delivery.[147] Nanofibers are generally developed using the electrospinning method, utilizing a range of materials, such as carbon, metal, metal oxides, polymers, and ceramics, which involves an electrostatic driving force to fabricate pure nanofibers. One significant characteristic that highlights the advantages of nanofiber-based ocular drug administration is the high surface area-to-volume ratio.[9,148] To improve the topical ophthalmic distribution of itraconazole, polymeric nanofibers of the drug were fabricated by S. Mehrandish *et al.* (2022) and then incorporated within ocular inserts. Polyvinyl alcohol–cellulose acetate and polycaprolactone–polyethylene glycol-12 000 copolymer composites were applied to electrospin three distinct nanofiber-based formulations.[149]

6.1.9. Cubosomes. Cubosomes are liquid crystal-based nanoparticles fabricated when amphiphilic surfactants (like glycerol monoolein and phytantriol) disperse and stabilize the cube-shaped lyotropic liquid crystalline phases. These surfactants undergo self-assembly to form bilayers around bicontinuous, non-intersecting aqueous channel networks during saturation with water, forming the intricate three-dimensional cubic phase isotropic configuration, having a precise and articulated architecture, making these nanosystems appropriate for drug encapsulation and release.[133,150,151] Several amphiphilic, hydrophobic, or hydrophilic compounds can be encapsulated in cubosomes due to their beneficial surface area and superior structural stability. Cubosomes have been studied for ocular administration of drugs, considering that their bilayer structure has characteristics similar to the static ocular barriers, such as the bilipid membrane of the corneal epithelium.[152] M. Said *et al.* (2020) used a melt-dispersion emulsification approach to develop chitosan-coated cubosomes loaded with voriconazole to modulate the drug-releasing rate, extend retention duration of formulation onto the ocular surfaces, and improve the drug transcorneal penetration as demonstrated by *in vivo* studies performed on New Zealand albino rabbits and consequently, therefore enhancing the ocular bioavailability by 171.15%. The optimized chitosan-coated cubosomes show promise as an ocular delivery technique for voriconazole.[153]

A comparative description of various nanocarrier systems explored for ocular antifungal drug delivery is summarized in Table 2, highlighting their respective benefits in enhancing solubility, permeability, retention, and therapeutic efficacy, as well as their inherent disadvantages, including stability concerns, toxicity risks, scale-up challenges, and potential ocular irritation. Furthermore, Table 3 summarizes various studies on nanosystem-based ocular azole delivery approaches aimed at developing and characterizing efficient strategies for managing ocular fungal infections.

6.2. Emerging devices and techniques for ocular drug delivery

Significant progress has been made in the domain of ocular medication administration in recent times, largely due to the

Table 2 Comparative overview of different nanocarrier systems, outlining their benefits and limitations in ocular antifungal therapy

Nanosystem	Advantages	Limitations
Polymeric nanoparticles	High drug loading, controlled release, biocompatible lipids and polymers (PLGA, chitosan), high scalability potential, targeted drug delivery, prevents non-specific distribution and drug degradation	Ocular clearance by tear turnover, possible burst release due to high surface area, particle aggregation, cytotoxicity limitations
Liposomes	Biocompatible and non-toxic, the amphiphilic nature allows both hydrophilic and lipophilic drug loading, enhancing corneal penetration and contact time by modifying the liposomal surface	Stability issues (fusion, leakage), rapid clearance, high production cost, and scalability limitations due to low stability
SLNs	Protects labile and lipophilic drugs, provides long-term stability, controlled release, good ocular tolerance, and targeted drug delivery due to easy surface modifications	Limited drug loading, drug expulsion during storage
Nanomicelles	Excellent solubilization of hydrophobic drugs, forms aqueous solutions of hydrophobic drugs, nano-sized range (<100 nm), enhances corneal penetration of topically administered drugs, and targeted drug delivery to intra-ocular tissues	Low drug loading capacity for hydrophilic drugs, rapid dilution in tear fluid, deformation and disassembly, poor scalability due to high cost, and toxicity due to surfactants
Dendrimers	High surface functionality, monodispersity, enhanced encapsulation of both hydrophilic and hydrophobic drugs, mucoadhesion, capacity for drug conjugation, and targeting	Potential cytotoxicity due to chemical modifications of the drug molecule, complex synthesis involves multiple steps, therefore, scalability limitations
Niosomes	Better stability than liposomes, low toxicity, and mucoadhesive properties due to non-ionic surfactants, good ocular penetration, potential scope for structural and surface modifications, and enhances ocular bioavailability	Lower entrapment efficiency and drug loading, vesicle fusion leading to leakage of encapsulated drugs, and high production cost due to the requirement of specialized equipments
Microemulsions and nanoemulsions	Microemulsions are thermodynamically stable, whereas nanoemulsions are thermodynamically unstable, characterized by a small droplet size, a high surface area, high solubilization of both hydrophobic and hydrophilic drugs, non-irritancy, and ease of scale-up	High surfactant concentration required for microdroplet stabilization may result in ocular irritation risk; nanoemulsions have a risk of phase separation
Nanosuspensions	Increase inherent solubility, ocular bioavailability, and dissolution rate of poorly water-soluble drugs, improve residence time in the cul-de-sac, and simplify preparation	Physical instability (aggregation, sedimentation), toxicity due to the use of surfactants
Nanofibers	High surface area, sustained release, targeted ocular delivery, and customized ocular permeation, potentially facilitated by fiber modifications, may enable the use of ocular inserts/patches	Limited clinical translation, ocular irritation, and manufacturing challenges because of multilayered structures
Cubosomes	Bioadhesive, high surface area, improves ocular bioavailability, and can encapsulate diverse drugs with high loading potential	Low efficiency in encapsulating hydrophilic drugs as compared to hydrophobic drugs, risk of aggregation, and large-scale production issues

development of novel devices designed to enhance treatment effectiveness and accuracy. One such innovation that has drawn interest is the drug-eluting contact lens, which may be used to offer treatments for conditions affecting the anterior portion of the eye, such as fungal keratitis.[165] Contact lenses, traditionally used for vision correction, are now utilized as three-dimensional, polymer-based, curved discs that are designed to fit and adhere easily to the cornea through surface tension. Drug-eluting contact lenses reduce the dose frequency range and adverse effects, while also improving ocular drug bioavailability and prolonging drug residence duration (approximately 10 times longer than conventional eye drops). Furthermore, they can be withdrawn if the therapy were to be discontinued. Typically, contact lenses are soaked in drug solutions for loading the drugs into the lenses.[9] A. Wong *et al.* (2022) explored the ocular administration of econazole utilizing a combination drug delivery system that included cyclodextrins along with soft hydrogel-based contact lenses, which considerably improved drug dissolution and penetration. The results showed that hydrogel-based lenses presented 2.8 times better medication delivery to the cornea than standard ophthalmic formulations, with cyclodextrins improving delivery by 5-fold, and thus achieving superior efficacy and therapeutic drug concentrations against fungal keratitis.[166]

The increased duration of contact on the cornea for drug absorption may be possible with drug-eluting contact lens devices. Nevertheless, it remains challenging to transport active compounds with undesired physicochemical properties, such as high molecular weight, low partition coefficient, and poor penetration.[165] These drawbacks have been effectively

Table 3 List of research studies utilizing diverse nanosystem-based formulations for the ocular delivery of azole derivatives targeting fungal eye infections

Formulation	Drug	Components	Method of preparation	Study outcomes	References
Nanoparticles	Fluconazole	Poly (ε-caprolactone), polyethylene glycol	Solvent evaporation method	The developed formulations exhibited PDI values between 0.27 and 0.38, indicating a narrow and uniform particle size distribution. Further, the optimized nanoparticle formulation demonstrated a mean particle size of 145.5 nm, a zeta potential of −29.23 mV, and an entrapment efficiency of 98.2%. In comparison with the pure drug, the optimized formulation demonstrated improved antifungal efficacy against *C. albicans*, characterized by a negatively charged surface, a sphere-like shape, and high drug entrapment efficacy. Furthermore, the developed ocular nanoparticle formulations exhibited a controlled *in vitro* drug release profile, with 84.89% of the drug released over 8 hours	123
	Luliconazole	Chitosan and Poloxamer 407	Ionic gelation followed by high-pressure homogenization	When compared with the pure drug solution, chitosan-based nanoparticle formulations were found to have a positively charged surface, along with dramatically improved precorneal retention as well as mucoretention. The particle size of the optimized formulation was found to be 216.6 nm, and PDI was found to be 0.2. With prolonged ocular release of luliconazole, the optimized formulation demonstrated extended exposure and enhanced ocular tolerance, achieving 88% release at 10 h, following release kinetics consistent with the Korsmeyer–Peppas model. The results obtained support that the nanoparticle formulations can be used as an appropriate option for the treatment of ocular fungal keratitis	154
Solid lipid nanoparticles	Fluconazole	Compritol 888 ATO, Precirol ATO 5, Phospholipon 90 G (Soya Lecithin)	Hot high-pressure homogenization	The nanoparticles exhibited a homogeneous particle size distribution of 138 nm, a PDI of 0.271, a low zeta potential of −2.07 mV, and a high entrapment effectiveness of 62.09% due to PEG inclusion. The formulation demonstrated a controlled drug release, with 67% of the drug released over 24 hours, and showed 1.5 times higher corneal permeation compared to the commercial fluconazole eye drop (0.3% w/v). Stability studies proved its durability during autoclaving and long-term storage. Furthermore, the SLNs demonstrated potent antifungal activity against *C. albicans*, including antibiofilm effects and excellent tissue penetration	155

Table 3 (*Contd.*)

Formulation	Drug	Components	Method of preparation	Study outcomes	References
Liposomes	Fluconazole	Hyaluronic acid, phosphatidylcholine, Triton-X100, Caproyl-90	Lipid film hydration technique	The optimal formulation showed enhanced entrapment efficacy of 42.82 ± 1.67%, with a particle size of 218.51 ± 4.5 nm, PDI of 0.49 ± 0.015, and zeta potential of −42.8 mV. In contrast to the pure fluconazole suspension and conventional liposomal formulation, the developed system exhibited superior corneal penetration in *ex vivo* and *in vivo* studies, along with a sustained drug release profile *in vitro*, showing only 47.1% release within the first hour and maintaining prolonged release for up to 24 hours	129
Niosomes	Fluconazole	Eudragit (RS100/RL100), hydroxypropyl-β-cyclodextrin, hydroxypropyl methyl cellulose (HPMC), Poloxamer 407	Thin film hydration method	The optimized formulation demonstrated particle size of 392.8 ± 27 nm; PDI of 0.74; and zeta potential of 28.5 ± 5 mV. Further, the formulations showed improved encapsulation efficiency (∼61.7%), prolonged release, and improved corneal penetration, with acceptable ocular tolerability, which were all demonstrated by the produced niosomal formulations. Furthermore, effective inhibition of the growth of *C. albicans* indicates that the formulations could potentially overcome fungal resistance by avoiding drug efflux processes	156
	Itraconazole	Chitosan, hyaluronic acid	Coacervation phase separation method	With their ideal vesicle size range between 160 to 350 nm, and PDI ranging from 0.194 to 0.362, the bioadhesive niosomal formulations showed effective chitosan and hyaluronic acid coating, leading to an improved ITZ release profile (80.5–90.5% at 24 hours) and effective entrapment (up to 86.5%). These characteristics demonstrate their suitability for long-term medication administration to ocular tissues. The formulations exhibited greater antifungal activity with considerably broader zones of inhibition ($p < 0.05$) than other control formulations, and *ex vivo trans*-corneal permeability indicated an optimum flux	157
	Fluconazole	Span 60, cholesterol, carbopol	Thin film hydration method	The most effective niosomal formulations included 1% w/w carbopol 934-based gel incorporated with niosomes that contained 0.3% w/w drug, which was developed with Span 60 and cholesterol in a 5 : 5 molar ratio. The selected formulation exhibited a vesicle size of 117.13 nm, zeta potential of −45.37 mV, and entrapment efficiency of 63.21%. Further, the formulation demonstrated a sustained drug release of 65.33% over 12 hours	134
Nanomicelles	Posaconazole	TPGS, Poloxamer 407, Poloxamer 188	Thin film hydration method	The nanomicelles exhibited a particle size ranging between 11.5–14 nm with a PDI range of 0.025–0.160, indicating a highly uniform distribution. Additionally, the zeta potential values were close to zero or slightly negative. The optimized *in situ* gel exhibited viscoelastic properties, forming a gel at physiological temperatures, with 90.97% drug content and a gelation temperature of 31.57 °C. *In vitro* drug release study showed that at the end of the 3rd	158 and 159

Table 3 (*Contd.*)

Formulation	Drug	Components	Method of preparation	Study outcomes	References
				hour, the nanomicellar gel systems released a total of 71.64% of the drug. Furthermore, the formulation demonstrated high antifungal activity, significantly reducing *C. albicans* populations compared to controls. *Ex vivo* studies confirmed superior drug absorption across corneal and scleral barriers compared to diluted Noxafil® oral suspension, while HET-CAM toxicity tests indicated excellent ocular safety	
	Voriconazole	Pluronic P123, Pluronic F68, Labrasol	Water addition/solvent evaporation method	The optimum acceptance rating was found for a proposed ideal formulation that included a 1 : 1 ratio of weight pluronic polymers, 2% w/v of labrasol, and a total pluronics to voriconazole weight ratio of 22.8 : 1. The optimized formulation exhibited excellent solubilization efficiency (98.0%), a small micellar size of 21.8 nm, and favorable stability parameters, with a zeta potential of −9.0 mV and a PDI of 0.261. Fungal susceptibility evaluations demonstrated better and more persistent suppression of *C. albicans* growth than standard voriconazole suspension, while histopathological investigations validated the optimum ophthalmic tolerability of the micellar formulation	160
	Voriconazole	Pluronic F127, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[maleimide(poly ethyleneglycol)-2000] (Mal-PEG2000-DSPE)	Injection technique	A maleimide-based micellar formulation enhances ocular drug absorption, offering a higher drug loading capacity and reduced cytotoxicity compared to pure voriconazole. A mixed micellar system was initially developed using Pluronic F127 and phospholipid, and subsequently functionalized with maleimide groups. These maleimide moieties can covalently react with the sulfhydryl groups of mucin present in the ocular mucus layer, thereby enhancing mucoadhesion and prolonging drug residence time on the ocular surface. The optimized formulation exhibited a particle size of 84.45 nm, a PDI of 0.22, and a zeta potential of −20.3 mV, while also achieving an excellent encapsulation efficiency of 95.33%. The formulation exhibited sustained drug release, with Mal-VCZ-MM showing a cumulative release of 90.54% within 12 hours. The uptake of coumarin-6 (a fluorescent marker) loaded maleimide-based micelles by HCE-T cells was 1.12 and 1.89 times higher than that of coumarin-6 loaded Pluronic F127-phospholipid-based mixed micelles and coumarin-6 solution, respectively. Maleimide conjugation increased ocular bioavailability and antifungal efficacy, with significantly greater anti-*C. albicans* potency	138

Table 3 (*Contd.*)

Formulation	Drug	Components	Method of preparation	Study outcomes	References
Nanoemulsion	Luliconazole	Capryol 90, Cremophor® RH 40 and Transcutol® P	Spontaneous emulsification approach	The luliconazole-loaded nanoemulsion formulation, optimized using central composite design-response surface methodology (CCD-RSM), efficiently entrapped the drug in a nano-sized lipidic core (18.43 ± 0.05 nm), resulting in a significant entrapment effectiveness (98.37 ± 0.47%) and stability over at least 2 months. The PDI and zeta potential of the optimized nanoemulsion were found to be 0.070 ± 0.008 and −0.202 ± 0.08 mV, respectively. It displayed increased antifungal efficacy and ocular biodistribution, with considerably greater concentration of drug in the cornea than luliconazole suspension. *In vitro*, ∼80% of the drug was released from the NE formulation over 96 h, following Higuchi kinetics. The optimized nanoemulsion efficiently permeated across the cornea and conjunctiva to transport the drug to deeper ocular tissues, indicating a potential to treat fungal endophthalmitis and keratitis effectively	161
	Itraconazole	Tween 80, Eumulgin CO40	Spontaneous emulsification approach	The nanoemulsion formulation demonstrated a promising strategy to overcome the poor ocular bioavailability of hydrophobic itraconazole following topical ocular administration. The two optimal formulations selected using pseudo-ternary diagrams and DOE demonstrated thermodynamic integrity, with globule dimensions of 223.5 ± 10.7 nm and 157.5 ± 14.2 nm. The mean zeta potentials of the two formulations were −9.2 ± 0.4 and −0.623 ± 0.04 mV. The nanoemulsion-based formulation achieved approximately 7-fold greater drug release within 60 hours compared to the pure drug solution, with improved ocular absorption, prolonged release, and increased ocular retention time. However, further research is needed, including ocular toxicity and *in vivo* experiments	143
SNEDDS	Voriconazole	Isopropyl myristate, Tween 80, Span 80	Thermal solubilization and mixing method	The optimal voriconazole-incorporated SNEDDS demonstrated a droplet size of 21.47 nm and a PDI of 0.157, resulting in considerably higher transcorneal permeation coefficients of 1.983×10^{-6} cm s^{-1} when compared with 1.166×10^{-6} cm s^{-1} for the marketed formulation. The corneal hydration levels determined using the desiccation approach demonstrated an acceptable range of 77.32% as compared to 78.74% for the marketed formulation, indicating minimal ocular injury. Under extreme conditions, the optimum SNEDDS formulation did not undergo phase separation or precipitation of the drug in a concentrated state	144

Table 3 (*Contd.*)

Formulation	Drug	Components	Method of preparation	Study outcomes	References
Nanosuspension	Itraconazole	Eudragit RS-100	Solvent evaporation method	The formulated nanosuspension was reported to have entrapment effectiveness ranging between 61.36 ± 1.34% and 76.34 ± 2.06%, a zeta potential of +0.608 to +16.4 mV, and particle size ranging from 332.8 to 779.3 nm. The optimal itraconazole nanosuspension achieved greater ocular absorption than the standard marketed formulation and itraconazole ophthalmic drop, as demonstrated by *ex vivo* ocular permeability assessment. Additionally, compared to the marketed itraconazole ophthalmic drop, the optimized nanosuspension-based formulation was found to be significantly more effective against *C. albicans* and *A. flavus*	146
	Voriconazole	Eudragit RS 100, polyvinylpyrrolidone	Quasi-emulsion solvent Evaporation method	Zetasizer and transmission electron Microscope evaluations of the optimized voriconazole-incorporated nanosuspension indicated homogeneous sphere-shaped composition devoid of aggregation. The well-dispersed nanoparticle, with a particle size range of around 137 ± 1.3 nm, exhibited a positive zeta potential between 22.6 and 31.4 mV, along with a significant entrapment efficiency of 98.5 ± 2.6%, indicating distinct physical stability. Compared to standard voriconazole injection, the formulation had a greater inhibitory action against *C. albicans* at reduced concentrations (2.5 μg mL^{-1}, $p < 0.05$). Further, *in vivo* studies on rat models showed improved corneal permeation	162
Nanofibers	Itraconazole	Polyvinyl alcohol-cellulose acetate, poly(ε-caprolactone)-polyethylene glycol 12 000	Electrospinning	The average dimensions of nanofibers ranged from 137 to 185 nm, and their compositions were found to be stable. The optimized formulations demonstrated favorable tensile strength (2.3–3.7 MPa) and flexibility. Considering cell viability of more than 70%, the formulation showed optimal antifungal action against *A. fumigatus* and *C. albicans*. As determined by *in vitro* release studies, sustained drug release was maintained (50–70%) for 55 days. According to the findings, the nanofibers may deliver itraconazole for an extended period, which reduces the need for frequent dosing	149
Cubosomes	Ketoconazole	Glyceryl-mono-oleate, Pluronic F127	Top-down method	Due to the stabilizing action of polyvinyl alcohol, the cubosomal formulation exhibited the highest entrapment efficacy of 82% and a particle size range of 35.5 ± 3.07 to 328.4 ± 7.94 nm. A reduced dosage frequency was demonstrated by the improved corneal retention duration and prolonged release profile, with approximately 73% of the drug released over 24 hours. *In vivo* studies showed no ocular irritation or toxicity in rabbits, confirming the	163

Table 3 (*Contd.*)

Formulation	Drug	Components	Method of preparation	Study outcomes	References
				formulation's safety for ocular administration. In addition, *in vitro* and *in vivo* studies indicated improved antifungal efficacy against *C. albicans*, supporting its potential for clinical application	
	Voriconazole	Hyaluronic acid, phytantriol, Pluronic F127	Top-bottom method	The optimized cubosomal *in situ* gel formulation exhibited a particle size of 71 nm, a drug flux of 6.5 μg (cm^{-2} h^{-1}), a zeta potential of −26.3 mV, and an entrapment efficiency of approximately 67%. In comparison to the pure drug aqueous suspension and optimal cubosomal dispersion, the optimized *in situ* gel formulation showed improved *ex vivo* ocular penetration, an *in vitro* drug release profile with a drug release of 89% after 12 hours, and antifungal activity, leveraging the multifunctional antifungal and mucoadhesive properties of hyaluronic acid	164

addressed by microneedle technology, a promising minimally invasive strategy offering the advantages of simplified drug administration, controlled release, and cost-effective manufacturing. Microneedle-based ocular-drug delivery technology also shows promise as a possible alternative to invasive subconjunctival injections. Microneedle arrays are made up of 50–1000 μm needles spread out over an area of 0.5–1.5 cm^2. They can be fabricated from materials including metals, ceramics, silicon, or polymers and are classified as solid, hollow, or dissolvable. Due to their conventional designs and ability to penetrate the scleral layer to a limited depth, microneedles can effectively deliver drugs without causing significant harm to the deeper ocular structures.[9,102] The goal of the study was to formulate an itraconazole-containing inclusion complex conjugated with β-cyclodextrin to increase the drug absorption for the treatment of fungal keratitis.

Furthermore, they developed a dissolving microneedle system using polyvinyl pyrrolidone and polyvinyl alcohol as polymeric materials, integrated with the inclusion complex, which significantly enhanced drug dispersion by up to four times. According to *ex vivo* research, 75.71% of the drug penetrated pig corneas in 24 hours, suggesting that this delivery approach has the potential for efficient ocular administration without causing any discomfort.[167] In another study, P. Suriyaamporn *et al.* (2022) developed fluconazole microemulsion-incorporated, two-layered dissolving microneedles for ocular delivery, designed using a simplex-lattice approach. The external layer was composed of 3% chitosan and 20% polyvinyl alcohol with a weight ratio of 1 : 4, and the inner layer of the microneedle system consisted of a drug-loaded microemulsion containing Tween 80, polyethylene glycol 400, eugenol, and water.[168]

Ocular inserts are an innovative ocular delivery device with a zero-order release profile, based on biodegradable polymers. These drug-coated ocular systems are sterile, solid or semi-solid, single or multilayered, and intended to be inserted into the conjunctival cul-de-sac of the eye. Ocular inserts have been employed for the treatment of conditions in both the anterior and posterior segments of the eye.[114] El-Emam *et al.* (2020) developed ocular inserts incorporating a proniosomal formulation of voriconazole using the film-casting technique. The voriconazole-loaded proniosomes were prepared using a coacervation phase separation approach, utilizing cholesterol and surfactants such as Span 80, Tween 80, Pluronic F127, or Span 60.[169] Another approach is to use ocular implants for the controlled administration of drugs to the posterior portion of the eye. However, it takes multiple injections or surgery, which comes with accompanying potential risks. These implantable ocular drug delivery devices are surgically inserted around intraocular tissues to manage chronic ocular conditions, regulating controlled drug efflux and, consequently, preventing the disease for a longer duration.[123,170]

6.3. Targeting strategies for enhanced ocular drug delivery

6.3.1. Polymers as structural agents for optimizing ocular bioavailability. Continuous research into nanosystems is crucial for developing optimal drug delivery systems for ocular

administration, aiming to achieve therapeutic levels of bioavailability. Alongside this, extensive studies are being conducted on various polymers, which play a pivotal role in the formulation of these advanced drug delivery systems. A wide range of synthetic organic biodegradable polymers are being engineered to safely, effectively, and sustainably transport therapeutic compounds to the various ocular sites, including polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), polylactic acid (PLA), polyglycolide (PGA), poly(lactic-*co*-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), poly(*n*-butyl cyanoacrylate) (PBCA), as well as their co-polymers.[171,172] Furthermore, the mucoadhesive and penetration-enhancing properties of various polymers demonstrate potential in increasing the viscosity of the tear film, thereby improving the retention of drugs in intraocular tissues and reducing unwanted systemic toxicities. Mucoadhesive polymers interact by forming covalent interactions with the mucin layer of the tear film. By increasing the viscosity of the tear film and exhibiting bioadhesive characteristics, the polymers enhance the therapeutic efficacy of the administered drug, prolong the formulation's accumulation at the application site, and significantly reduce lacrimal drainage or precorneal clearance.[173] I. A. Elbahwy *et al.* (2018) developed self-emulsifying drug delivery systems (SEDDS) having mucoadhesive properties with *S*-protected thiolated Eudragit® L100-55 to improve ocular retention duration and solubility of econazole nitrate. The SEDDS demonstrated high mucoadhesive characteristics and persistent drug release over 8 hours, plus there were no signs of ocular toxicity.[174] M. Alami-Milani *et al.* (2018) synthesized a PCL-PEG-PCL triblock copolymer using the ring-opening polymerization technique on ε-caprolactone, with the incorporation of PEG. This triblock copolymer was further utilized to formulate nanomicelles loaded with hydrophobic dexamethasone, aiming to enhance targeted drug delivery to intraocular tissues.[175] D. R. Kim *et al.* (2024) fabricated electrospun nanofibers using PCL incorporating dexamethasone acetate within the fiber matrix to facilitate targeted delivery of the drug to the posterior ocular portion.[176] In a study performed by N. Zaghloula *et al.* (2022), the spray drying technique was used to fabricate teraconazole (a triazole ketal derivative) – incorporated mesoporous silica carriers (Syloid 244 FP) modified with PLGA for ocular administration. The integration of PLGA was performed to obtain an optimized and sustained release profile of the drug.[177]

6.3.2. Chitosan-based nanoformulations for targeted ocular drug delivery. These highly biocompatible, non-cytotoxic, and diffusible cationic polysaccharides, comprising randomly dispersed D-glucosamine and *N*-acetyl-D-glucosamine subunits interconnected by β1-4 linkages, are derived from chitin and have been considered an appropriate vehicle for ocular therapeutics. Additionally, chitosan possesses mucoadhesive properties, making it a suitable option for enhancing the bioavailability of active therapeutic compounds and prolonging the drug residence time in the precorneal region. Chitosan, because of its cationic property, interacts with the negatively charged corneal and conjunctival ocular regions as well as negatively charged mucin, which may allow for interactions with the chitosan amino-groups and promote mucoadhesive properties.[178–180] Furthermore, the permeation-enhancing characteristics of chitosan enable it to dissolve across the tightly bound junctions within epithelial cells, thereby significantly increasing its penetration across ocular barriers.[181] S. R. Pardeshi *et al.* (2022) synthesized voriconazole-loaded nanoparticles that were integrated into a carboxymethyl chitosan-poloxamer *in situ* gel formulation, resulting in delayed drug release, higher antifungal activity against *C. albicans*, and better corneal penetration. The formulation demonstrated non-irritability and potential as an alternative to standard eye drops.[182] X. Sun *et al.* (2022) used a phenylboronic acid-modified chitosan oligosaccharide-vitamin E copolymer (PBA-CS-VE) to synthesize mucoadhesive nanomicelles containing voriconazole for the treatment of fungal keratitis (Fig. 8). *In vivo* studies in the rabbit model demonstrated that these nanomicelles exhibited significant mucoadhesion, enhanced corneal penetration, prolonged ocular retention, and improved therapeutic effectiveness compared to free drug formulations.[183] In another study, T. A. Ahmed *et al.* (2017) optimized ketoconazole-incorporated PLGA nanoparticles for ocular delivery by integrating them into alginate-chitosan *in situ* gels. When compared with pure drug solutions, the chitosan-modified formulations exhibited prolonged drug release, enhanced penetration, and increased antifungal activity, rendering them an effective therapy for ocular fungal infections.[184]

6.3.3. Stimuli-responsive nanoformulations for enhanced ocular drug delivery. Stimuli-sensitive nanosystems are polymer-based structures that respond rapidly to minuscule environmental variations. These smart systems engage with the specific surrounding stimuli by changing their size, shape, texture, and mechanical characteristics. Stimuli-responsive hydrogel systems, commonly employed as *in situ* gel formulations for ocular drug delivery, have been extensively studied due to their ability to undergo sol–gel phase transitions in response to specific ocular environmental conditions. These systems offer controlled drug release and a safe delivery mechanism, attributed to their optimized pH, suitable rheological properties (such as viscosity and gel strength), and physiological isotonicity.[185] Thermo-sensitive hydrogels alter their phase from solution to gel, as well as their structure, responding to the intraocular temperature (32–34 °C), which occurs due to increased hydrophobicity, intermolecular hydrogen bonding, change in polymer solubility or structure of polymeric network, and polymeric chain entanglement. A triblock copolymer, called poloxamers (including Poloxamer 407, Poloxamer 188, *etc.*), is widely used in research studies to develop thermo-responsive *in situ* gel-based formulations for ocular drug delivery. Poloxamers are copolymers made up of polyethylene oxide (PEO), which makes the hydrophilic segment surrounded by the hydrophobic polypropylene oxide (PPO) blocks.[185,186] The main reasons for the preference for hydrogel systems are their macro-porous organization and favorable swelling characteristics.[187] Malec *et al.* (2024) investigated fluconazole-containing micellar formulations that utilized Pluronic F127 to enhance antifungal activity against resistant strains of *Candida*. Formulations of 5 to 10% w/v Pluronic F127 (Poloxamer 407) improved drug

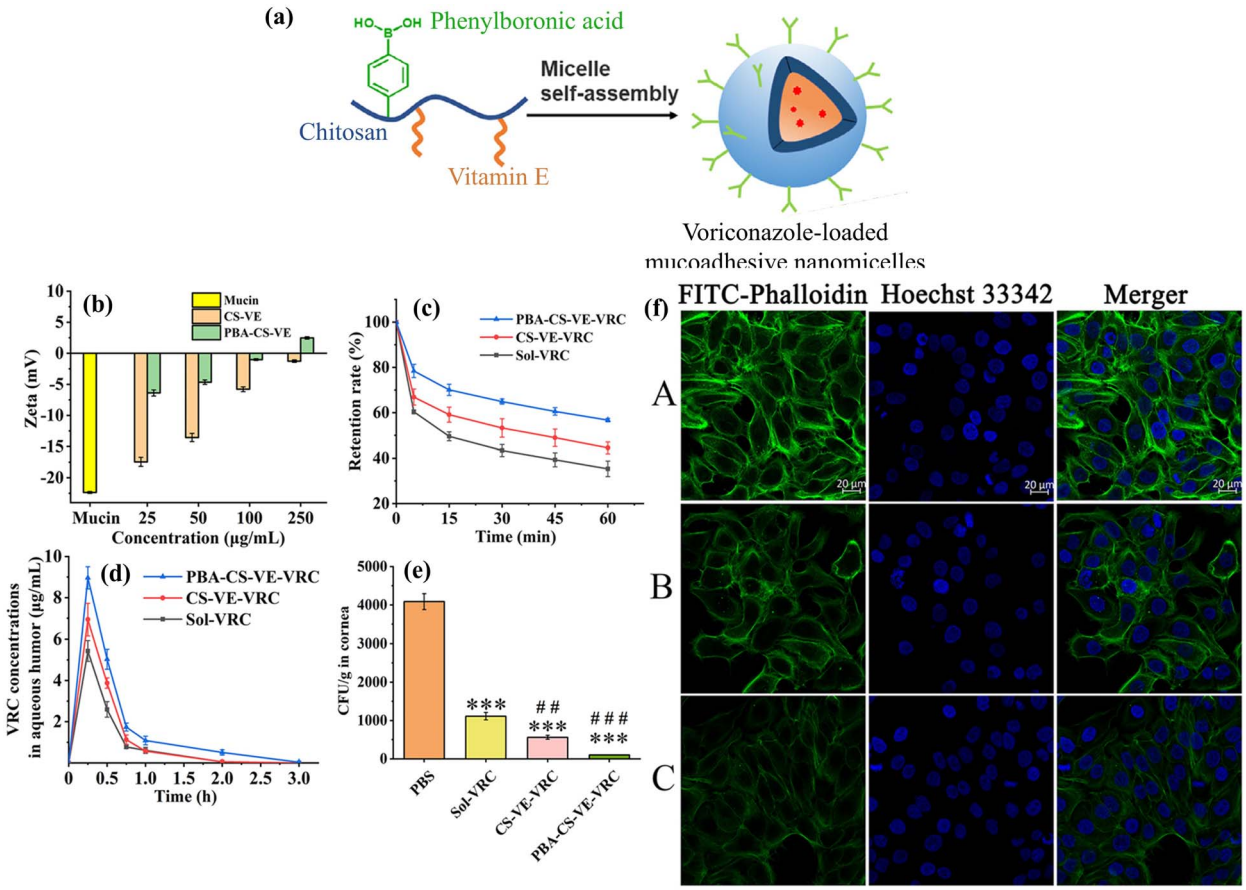

Fig. 8 (a) Diagrammatic representation of developing voriconazole-loaded PBA-CS-VE-based mucoadhesive nanomicelles; evaluation of mucin adhesion, ocular surface retention, and ocular pharmacokinetics/pharmacodynamics of the developed formulation. (b) Zeta potential analysis of mucin interacting with copolymers to assess electrostatic binding and mucoadhesive potential; (c) drug retention profile over time on isolated rabbit eyeballs, indicating formulation residence; (d) aqueous humor drug concentration–time curve in rabbits, reflecting ocular pharmacokinetics; (e) quantitative determination of fungal burden, represented as CFU per gram of corneal tissue; (f) CLSM visualization of F-actin organization in HCE-T cells following culture with H-DMEM (A), CS-VE (B) and PBA-CS-VE (C). Reproduced with permission from ref. 183.

dissolution and attenuated efflux pump function, which substantially improved the effectiveness of the drug. The temperature-responsive nature of the polymer enabled the formulations to undergo sol-to-gel transitions and maintain extended stability. These characteristics of poloxamer-based systems highlight their potential for improved antifungal therapy.[188]

Depending on the type of suspended group, pH-sensitive polymers can be broadly classified as anionic, cationic, or neutral polymers. These polyelectrolytes contain ionizable groups within their structure that can donate or accept protons in response to changes in the surrounding pH. The two most often researched pH-sensitive polymers in ocular drug delivery are chitosan and polyacrylic acid, also known as carbomer.[189] Although a pH of 7.4 in tear fluid can be utilized for pH-responsive drug delivery, variations may irritate the eye, causing increased tears and blinking, which in turn reduces the ocular bioavailability of drugs. In response to pH changes, the pH-responsive polymers disrupt the amphiphilic balance of the copolymers, leading to the disintegration of nanocarriers and the release of drugs. Polyacrylic acid, polycarbophils, cellulose acetate phthalate, and chitosan are examples of common ocular polymers.[190,191] H. Kolge *et al.* (2023) created fluconazole-loaded chitosan-PLGA nanoparticles, which achieved pH-sensitive prolonged release and about 8% loading of the drug. The formulation minimized drug efflux and cytotoxicity while increasing antifungal activity, demonstrating MIC reductions of 16 and 64 times against *C. albicans* and resistant *C. auris*, respectively.[192]

Through cross-linking with cations (Na^+, Ca^{2+}, and Mg^{2+}) in lacrimal fluid, ion-responsive polymers based ocular gels undergo sol-to-gel transformation; greater cation concentrations cause the polymer to become more viscous and thus, improve ocular retention time of the formulation. Gellan gum (Gelrite®/Kelcogel®) and alginic acid are two commonly used ion-sensitive polymers (polysaccharides) that form interactions with cations in the lacrimal sac to produce hydrogen-bonding and cross-linked complex systems, which create a conjunctival-scleral depot for prolonged drug release.[193] To improve dissolution and bioavailability, X. Huiyun *et al.* (2024) created an ion-sensitive *in situ* gelling system with sodium alginate and a ketoconazole-hydroxypropyl-β-cyclodextrin complex. The

formulation demonstrated improvement in drug release, corneal permeation, antifungal efficacy, and a 47-fold increase in corneal bioavailability.[194]

Furthermore, a mixture of polymers can be employed to achieve a diverse, stimuli-responsive approach, where more than one trigger is considered to transform the liquid state of an ocular formulation into a gel-like state when applied to the eye. Multiple stimuli-responsive *in situ* gelling advances can provide personalized and targeted ocular therapies. These formulations improve the release kinetics of drugs, ocular bioavailability, and patient compliance by utilizing a combination of ocular triggers.[195]

Infected inflammatory ocular tissues typically exhibit excessive ROS generation (approximately 10 times higher than in normal tissues), which can be utilized as a pathological trigger for site-specific drug release. One common compound that responds to ROS is polyethylene glycol-thioketide (PEG-TK). The thioketal (TK) bond, in particular, is considered to be one of the most efficient ROS-responsive moieties owing to its improved stability in biological environments and rapid breakdown, generating acetone and thiol moieties when exposed to significant ROS concentrations.[196,197] J. Yu *et al.* (2024) developed ROS-responsive UiO-66 based nanoparticles functionalized with UBI29-41 and PEG-thioketal for moxifloxacin delivery, demonstrating controlled drug release under oxidative stress with potential for targeted ocular therapy. It was possible to accomplish site-specific drug release because the PEG-TK coating on the outer layer of the nanoparticles served as a barrier that restricted drug release until the nanoparticles reached the infected tissue, which had an elevated level of ROS. Further, UBI29-41 imparted bacterial targeting characteristics to the nanoformulation. The developed nanoparticles demonstrated strong antibacterial and biofilm-eradicating activity against *S. aureus* and *P. aeruginosa in vitro*, as well as excellent therapeutic efficacy against bacterial endophthalmitis *in vivo* under ROS conditions.[198] In another study, P. Niu *et al.* (2023) used 4-carboxyphenylboronic acid pinacol ester as the ROS-responsive group to formulate a ROS-controlled release glycol chitosan-based polymeric nanocarrier, aiming to achieve effective voriconazole penetration through ocular barriers for the treatment of fungal keratitis (Fig. 9). 4-Carboxyphenylboronic acid pinacol ester serves as a ROS-sensitive linker, where the boronic ester moiety undergoes oxidative cleavage by hydrogen peroxide, generating phenolic derivatives and triggering drug release in high ROS environments.[199]

6.3.4. Ocular absorption enhancers. The hydrophilic–lipophilic properties of a compound influence its potential to permeate across the epithelial and endothelial layers of the cornea and conjunctiva, which form the main barrier for intraocular delivery of drugs, with epithelial penetration contributing up to 90% for lipophilic molecules. However, drug permeability across the stromal barrier primarily depends on the molecular size of compounds, rather than their hydrophilicity or lipophilicity. The stroma acts as a significant barrier for smaller-sized lipophilic compounds, those with a radius less than 10 Å. Nonetheless, penetration through the scleral layer is comparable to that of the corneal stroma. Lastly, the endothelial layer is dependent on both the hydrophilic–lipophilic balance and the molecular size, which follow the paracellular route of drug penetration.[200]

Cyclodextrin, a natural cyclic oligosaccharide, is generally complexed with drug compounds to improve the drug solubility without affecting the lipophilic property of the drug. The cyclodextrin structures consist of lipophilic voids and hydrophilic hydroxyl groups bonded to the exterior surfaces, where the lipophilic cavities develop guest–host interactive forces with lipophilic drugs in aqueous medium to form inclusion complexes. The lipophilic drugs reside within the internal cavity of cyclodextrins.[201] The encapsulated guest molecule can be liberated from the complex in the aqueous tear film by preferentially absorbing membrane lipids, such as phospholipids and cholesterol, and concurrently ejecting the drug. P. Suvarna *et al.* (2022) synthesized cyclodextrin-based ternary complexes of voriconazole and incorporated them into mucoadhesive films to improve solubility, transcorneal penetration, and antifungal activity against fungal keratitis. The optimal formulation increased drug solubility by 14-fold, transcorneal flow by 4-fold, and prolonged drug release.[202] Abd El-Gawad *et al.* (2017) used several ways to enhance the dissolution, ocular absorption, and bioavailability of econazole nitrate by fabricating inclusion complexes using β-cyclodextrin and hydroxypropyl-β-cyclodextrin. Phase-solubility characterization indicated a steady 1 : 1 molar complex, and with hydroxypropyl-β-cyclodextrin enhancing drug dissolution by around 4-fold compared to the pure drug alone.[203] In another study, B. Mahaling *et al.* (2016) demonstrated the influence of several permeation enhancers, including benzalkonium chloride, capric acid, ethylenediaminetetraacetic acid (EDTA), sodium glycocholate, and sodium taurocholate, on nanoparticle permeation across ocular barriers. The researchers developed polycaprolactone-based nanoparticles using the nanoprecipitation approach, followed by surface coating with chitosan, gelatin, and Pluronic F68. The influence of five different permeation enhancers was assessed individually by formulating nanoparticles with each enhancer separately and administering them as eye drops in one eye, while the contralateral eye received nanoparticles without enhancers as a control, thereby enabling comparative evaluation of their permeation efficiency. Based on the findings, Pluronic F68-coated nanoparticles demonstrated superior bioavailability across most ocular tissues, primarily attributed to their hydrophilic and mucoadhesive nature that favored transport *via* the conjunctival-scleral pathway. The study revealed that permeation enhancers mainly improved drug bioavailability in anterior eye tissues (cornea, conjunctiva, iris, and lens). Specifically, sodium glycocholate and sodium taurocholate enhanced corneal permeability by disrupting mucous, widening tight junctions, and altering membrane fluidity. Benzalkonium chloride and capric acid increased conjunctival permeability, while benzalkonium chloride and sodium glycocholate improved permeation to the iris and ciliary body by modulating epithelial barriers. In contrast, EDTA reduced nanoparticle bioavailability in the lens and choroid, and sodium glycocholate unexpectedly lowered delivery to the choroid and retina.[204]

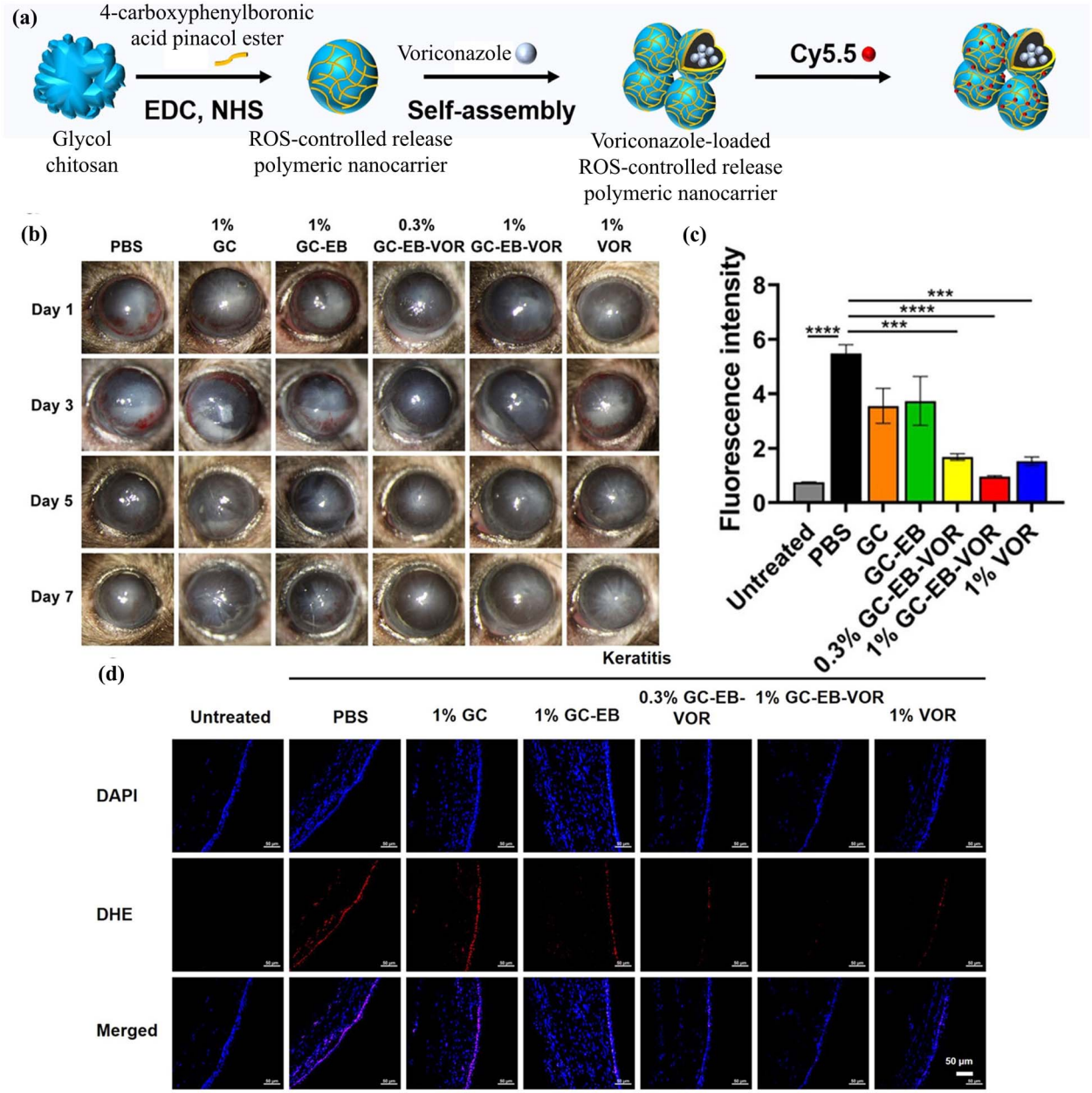

Fig. 9 (a) The development process of voriconazole-incorporated glycol chitosan-based ROS-responsive polymeric nanocarriers; *in vivo* therapeutic evaluation of developed formulations in a mouse model with fungal keratitis. (b) Time-dependent therapeutic response following topical administration of glycol chitosan-based nanocarrier and voriconazole eye drops, with PBS-treated mice (control). (c) Corneal sections stained with DHE (red, indicating ROS) and DAPI (blue, nuclei) to assess ROS modulation by different treatments. (d) Quantitative comparison of corneal ROS levels among the treatment groups. Reproduced with permission fromref. 199 under the Creative Commons Attribution-NonCommercial-NoDerivatives (CC BY-NC-ND) 4.0 license (https://creativecommons.org/licenses/by-nc-nd/4.0/).

6.4. Nanomedicine strategies to overcome resistance

In the ongoing struggle against resistance to azoles and other antifungal agents, nanoformulations have shown great promise as a novel approach that overcomes the drawbacks of conventional treatments. Because fungal pathogens are less likely to acquire resistance to these novel formulations, they are widely utilized in nanomedicine to treat bacterial and fungal diseases. Additionally, a variety of nanoparticles possess strong antifungal properties and may be considered as a substitute for treating various fungal infections.[205] The innovative characteristics of these novel formulations, including nano size range, adjustable hydrophilicity or lipophilicity, higher surface area-to-volume ratios, modifiable surface chemistries and the ability to interact at the molecular level with biological systems; facilitate enhanced efficacy of conventional antifungal drugs, enable circumvention of resistance mechanisms as well as offer opportunities to introduce novel antimicrobial modalities.[206] A promising strategy in combating fungal infections involves the

application of metal-based nanomaterials, including metallic nanoparticles and metal–organic frameworks. These systems are particularly advantageous as most microorganisms do not readily develop resistance against them, primarily because their antifungal activity arises from the generation of ROS within fungal cells, leading to the disruption of essential biological processes. The production of ROS acts as one of the fundamental approaches by which metal-based nanoformulations fight fungal infections. Various metals and metal oxides, such as silver (Ag), silver oxide (AgO_2), copper (Cu), copper oxide (CuO), calcium oxide (CaO), magnesium oxide (MgO), iron (Fe), zinc (Zn), zinc oxide (ZnO), silica (Si), gold (Au), titanium (Ti), titanium dioxide (TiO_2), palladium (Pd), *etc.*, have been investigated for their potential antifungal properties.[207,208] Metal-fungal interactions play a crucial role in fungal homeostasis and resistance. Interestingly, fungi themselves can serve as efficient biofactories for nanoparticle synthesis due to their scalability, cost-effective cultivation, and inherent metal resistance, thereby enabling the production of novel drug delivery systems with significant antifungal properties.[208] Ag, a transition metal, functions as a potent antifungal agent for the eradication of several fungal pathogens. Ag^+ ions have a great affinity towards phosphate and sulfhydryl (thiol) groups found in β-glucan synthase enzyme, which are involved in the formation of bacterial and fungal cell walls. Moreover, Ag could affect the electron transport chain and energy generation process.

Furthermore, Ag^+ inhibits DNA replication and the respiratory chain in bacterial and fungal cells, subsequently leading to cell death through the generation of ROS.[209] ZnO-based nanoparticles have also been shown to induce cytotoxicity by elevating ROS concentrations, which cause oxidative stress, cellular damage, and ultimately cell death. By interacting directly with the fungal cell membrane and affecting its interaction with the cell wall, ZnO nanoparticles have demonstrated notable suppressive characteristics against the development of *C. albicans*, which can further prevent growth and lead to cell death. Further, the interaction of these nanoparticles with fungal cells can disrupt their structural integrity and osmotic equilibrium, as well as reduce the number of oxidative enzymes and the effectiveness of their anti-oxidative defenses.[208,210]

Further, these nano-sized drug delivery systems (20–500 nm) play a critical role in overcoming biofilm-associated antifungal resistance. Their small size, especially below 500 nm, enables penetration through the dense extracellular matrix of fungal biofilms, reaching otherwise protected fungal cells. It is easier for smaller nanoparticles to penetrate through this complex biofilm network, which contains proteins, dense polysaccharides, and other components that block larger particles.[211] According to studies, by overcoming these constrained channels, nanoparticles of 40 nm in size, such as certain nanoemulsions, significantly increase the penetration of incorporated antifungal drugs into *C. auris* biofilms, which ultimately enhance the efficacy of drug delivery. Additionally, smaller nanomedicine, owing to their high surface-area-to-volume ratio, exhibit greater stability and diffusion within biofilm's aqueous channels, enabling uniform drug distribution. The surface charge of nanoparticles is also critical for biofilm penetration, with positively charged particles showing stronger interactions with the negatively charged polysaccharides and proteins of the biofilm matrix.[211,212]

Polymeric nanoformulations with appropriate engineering and surface modifications, such as coating with hydrophilic polymers like PEG, can enhance the local concentrations of antifungal drugs within the biofilm site by overcoming the biofilm's protective barrier. Polymeric nanoparticles can be engineered to deliver enzymes or toxins that degrade the biofilm matrix, enhancing drug susceptibility.[211] Polymeric nanocarriers can overcome drug resistance by encapsulating drugs, protecting them from enzymatic degradation by biofilm-forming microorganisms, and preserving their efficacy. Further, functionalization of these nanocarriers with ligands such as antibodies (such as anti-adhesion antibodies) or antifungal peptides to selectively target biofilm components or fungal surface structures, enhancing binding to biofilm matrix, reducing off-target effects, and increasing local drug concentration at the biofilm site.[213,214]

7. Limitations and challenges of nanoformulation-based azole delivery for ocular applications

Despite the significant therapeutic potential of nanocarrier-based azole formulations for ocular delivery, offering enhanced drug retention, improved corneal penetration, and sustained drug release, numerous limitations and unresolved challenges continue to impede their clinical translation, as evidenced by recent research.[132] Stability concerns such as Ostwald ripening, particle aggregation, drug leakage, and chemical degradation have been widely reported in the literature, posing significant challenges to the reproducibility, shelf life, and therapeutic efficacy of nanocarrier-based ocular delivery systems.[215] While some investigations report high biocompatibility, others indicate potential ocular irritation or adverse effects, which are often attributed to variations in nanoparticle size, surface characteristics, and excipient composition. The clinical translation of these systems is further complicated by the lack of well-established *in vitro–in vivo* correlation models and standardized evaluation protocols for safety and efficacy.[216] Additionally, achieving scalable manufacturing without compromising quality and reproducibility remains a substantial challenge. These challenges underscore the pressing need for ongoing research and comprehensive evaluation to ensure the safe and effective clinical application of nanoformulated azole therapies for ocular fungal infections. Furthermore, the transition from promising preclinical outcomes to clinical use is significantly impeded by regulatory ambiguities and the limited availability of long-term safety and stability data. This highlights the need for sustained multidisciplinary collaboration to bridge existing gaps and facilitate successful clinical translation.[132]

The cost-effectiveness evaluation between conventional treatment approaches and novel drug delivery systems is a critical paradigm that must be considered before drawing

definitive conclusions regarding the benefits and limitations of nanotechnology-based drug delivery systems. Conventional drug delivery approaches often appear less expensive when considering only drug acquisition costs; however, a comprehensive economic evaluation must also incorporate adverse event-related costs, hospitalizations, discontinuations due to toxicity, and differences in therapeutic response rates.[217] Conventional therapies available for ocular infections, although less expensive in terms of production and procurement, often result in higher cumulative costs due to poor ocular bioavailability, frequent dosing requirements, shorter therapeutic duration, and the need for repeated clinical interventions (*e.g.*, multiple instillations or invasive injections). These factors not only increase direct healthcare costs but also contribute to indirect costs through reduced patient adherence and higher complication management. Although nanocarrier-based formulations involve higher initial development costs, their ability to enhance retention, improve permeation, and sustain drug release reduces dosing frequency, adverse effects, and invasive interventions. This results in a more favorable cost-effectiveness profile than conventional drug delivery systems, where focusing only on acquisition cost underestimates the true economic value of nanomedicines.[218]

8. Conclusion and future perspective

The persistent challenges regarding the efficient management of ocular fungal infections emphasize the need for improved drug delivery approaches to overcome the limitations associated with conventional therapy. In this context, advancements in azole antifungals have emerged as a promising cornerstone for effective ocular antifungal treatments, addressing conditions such as fungal keratitis, endophthalmitis, scleritis, conjunctivitis, and blepharitis. This antifungal family has encountered numerous challenges, the majority of which were subsequently overcome by formulation techniques; however, for more favorable outcomes, certain preclinical (strong *in vitro–in vivo* relationship) and clinical (resistance, cross-resistance, and recurrence) concerns remain to be addressed.

The insufficient availability of US-FDA-approved ophthalmic formulations incorporating azole antifungals for the pharmacotherapy of fungal eye infections, despite studies investigating the development of novel dosage formulations, ultimately results in the off-label and non-optimized use of azoles, which also elevates the risk of resistance and cross-resistance. Furthermore, the unavailability of marketed azole-based dosage forms for ocular fungal infections restricts access to suitable comparators for assessing the effectiveness and potency of newly developed ocular formulations under research. Despite ongoing formulation advancements, significant knowledge gaps remain in understanding long-term ocular tolerability, pharmacokinetics, and patient-specific responses to azole-based therapies. Future research should also explore regulatory pathways for ophthalmic nanosystems, addressing challenges related to scale-up, stability, and compliance with ICH and FDA guidelines, to ensure safe and effective clinical translation. This highlights the need for targeted research to transfer innovative azole-based ocular therapies from the laboratory to consumers. To successfully implement these nanosystem-based strategies in the clinical field, future studies should focus on addressing key issues, including stability, scalability, regulatory compliance, and patient-specific modifications. In addition to formulation-related complications, resistance and cross-resistance must be addressed. These limitations can be overcome by designing newer azole derivatives with superior characteristics, broad-spectrum antifungal action, and synergistic combinations to address resistant pathogens, decrease doses, and reduce toxicity.

Overall, bridging the gap between laboratory studies and clinical implementation will need cooperation from pharmaceutical researchers, physicians, and regulatory bodies. The discipline is well-positioned to develop effective, secure, and patient-focused treatments for challenging ocular fungal diseases by adopting such innovations, which will ultimately enhance the quality of life for patients.

Author contributions

D. S., R. G., D. K.: investigation, methodology, writing-original draft, data curation; M. K.: conceptualization, supervision, resources, formal analysis, writing-original draft, validation; M. A. M.: conceptualization, project administration, funding acquisition, supervision; formal analysis, writing-review & editing; M. T., A. M. A., G. O. E.: visualization, validation, writing-review & editing. All authors reviewed the manuscript.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No new experimental data, software, or code were generated or analysed in the preparation of this review. All relevant information, including data presented in figures and tables, has been obtained from previously published studies, which are cited throughout the article.

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