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Perspective

Zeolitic Imidazolate Frameworks as Therapies for Fungal Keratitis

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DESCRIPTION

Fungal keratitis, often caused by *Aspergillus fumigatus*, *Fusarium solani*, or *Candida albicans*, represents a serious ocular infection leading to corneal inflammation, scarring, and potential vision loss. Traditional treatments, such as topical natamycin or amphotericin B, are often hindered by poor corneal penetration, limited bioavailability, and frequent dosing requirements. This has spurred the search for novel delivery systems to enhance therapeutic success. Zeolitic Imidazolate Frameworks (ZIFs)-particularly ZIF 8 and ZIF 90-offer promising platforms due to their porous architecture, controlled release properties, and dual-target therapeutic mechanisms.

ZIF 8 and ZIF 90 are metal-organic frameworks consisting of zinc ions coordinated with imidazolate ligands. Their crystalline, porous structure resembles that of zeolites, with tunable pore sizes and surface chemistry. ZIF 8 typically uses 2-methylimidazole ligands and degrades under acidic conditions, whereas ZIF 90 incorporates imidazole-2-carboxaldehyde, which introduces aldehyde functionalities and enhances biocompatibility. These frameworks can be engineered at the nanoscale to encapsulate antifungal molecules, control sustained drug release, and interact with infected tissues in a controlled fashion. Their biodegradability in mildly acidic microenvironments-such as those found in inflamed corneal tissue-makes them ideal for targeted ocular therapy.

ZIF 8 nanoparticles have demonstrated fungicidal activity against filamentous fungi and yeasts through direct interaction with cell walls and membranes. Contact between ZIF 8 particles and fungal spores leads to membrane disruption, leakage of cellular contents, and impaired hyphal growth. Importantly, this contact-mediated antifungal effect does not rely solely on loaded drugs but stems from the nanoscale framework's physical and chemical properties. Beyond standalone activity, ZIFs serve as carriers for existing antifungals like natamycin. Encapsulation of natamycin within ZnO-decorated ZIF 8 or ZIF 90 particles allows for pH-triggered drug release: in the acidic environment of infected cornea, nanoparticles disassemble and release antifungal payload gradually. This approach reduces the dosing frequency, provides sustained therapeutic levels, and enhances fungal kill through combined mechanical, chemical, and pharmacological mechanisms. ZIF 90 exhibits not only antifungal capacity but also immune-regulatory actions. In ocular models, ZIF 90 suppresses inflammatory cytokine secretion and promotes controlled macrophage apoptosis. This modulation prevents excessive neutrophil infiltration, reduces collateral tissue damage, and supports corneal healing. ZIF 90 typically shows superior cellular tolerance compared to ZIF 8, minimizing cytotoxic effects on corneal epithelium and resident immune cells.

Toxicity assessments in laboratory-grown corneal epithelial cells and immune cell cultures demonstrate that both ZIF 8 and ZIF 90 are tolerated at therapeutic concentrations. ZIF 90, in particular, shows fewer adverse effects and minimal disruption to epithelial integrity. On the ocular surface, topical application of ZIF therapies typically produces no visible irritation, conjunctival redness, or shedding of epithelial cells when used intermittently over short durations.

Long-term safety remains a key area of investigation, especially regarding repeated administration, nanoparticle clearance, and any potential for accumulation in ocular tissues. Designing ZIFs that respond to specific triggers such as increased Reactive Oxygen Species (ROS), enzymatic activity, or even fungal-specific signals could enable dynamic, on-demand antifungal delivery tailored to infection severity. Embedding emerging antifungals or antimicrobial peptides within ZIF architectures may enhance spectrum coverage and reduce risk of resistance development. Integrating ZIF particles into contact lens material or coatings can offer continuous, sustained drug delivery for prolonged keratitis treatment without frequent application. Pilot studies combining *in vitro* infection models, animal experiments, and controlled human safety testing will be essential to confirm therapeutic efficacy, tolerability, and formulation stability.

CONCLUSION

Zeolitic Imidazolate Frameworks-specifically ZIF 8 and ZIF 90-show remarkable promise as dual-action therapeutic platforms for fungal keratitis management. By combining antifungal potency, immune modulation, and targeted drug release, these frameworks address key limitations of traditional antifungal eye drops. Early studies highlight their capacity to reduce fungal

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burden, minimize inflammatory damage, and promote corneal healing with excellent tolerance in ocular tissues. While further refinement, translation studies, and clinical validation are required, ZIF-based therapies hold the potential to revolutionize care for fungal keratitis-particularly in settings where standard treatments are less effective or accessible. Their versatility, scalability, and multifaceted modes of action position them as next-generation ocular nanomedicines capable of improving patient outcomes in vision-threatening fungal infections.