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Mucoadhesive Ocular Inserts for the Treatment of Fungal Keratitis: Biopolymer Engineering and Unidirectional Drug Delivery Strategies

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ABSTRACT

Background: Fungal keratitis is a sight-threatening corneal infection that hits hardest in tropical, agrarian regions, with an estimated one million or more new cases every year. Treatment still leans on antifungal eye drops that wash away within minutes. Fewer than 5% of an instilled dose typically reaches the intraocular tissues, so patients are asked to dose hourly, for weeks, and adherence suffers.

Objective: This review examines whether biopolymer-based mucoadhesive ocular inserts, particularly those engineered for unidirectional (cornea-facing) release, can overcome the precorneal and corneal barriers that limit topical antifungal therapy, using fluconazole as the model drug.

Methods: Literature on ocular barriers, fungal keratitis, fluconazole, ocular inserts, mucoadhesive biopolymers, directional release, formulation, characterization and preclinical evaluation was surveyed from PubMed, ScienceDirect, Scopus and Google Scholar and synthesized into comparative tables.

Key Findings: Chitosan, alginate, hyaluronic acid and cellulose derivatives provide the hydration, chain mobility and functional groups needed for adhesion to the ocular mucin layer, and chitosan adds antimicrobial and permeation-enhancing effects. Fluconazole-loaded nanoparticles, niosomes, nanogels, in situ gels and freeze-dried chitosan inserts have improved corneal permeation, retention and aqueous humour exposure in animal models. Drug-impermeable backing layers, borrowed from buccal patches, can steer release toward the cornea, although ocular evidence remains limited.

Conclusion: Mucoadhesive, unidirectional ocular inserts are a rational platform for fluconazole delivery in yeast keratitis. Their clinical future depends on reproducible directional release, patient comfort, validated sterilization and well-designed clinical studies.

Keywords: Fungal keratitis; Fluconazole; Ocular insert; Mucoadhesion; Chitosan; Biopolymers; Unidirectional release; Backing layer; Corneal permeation

1. INTRODUCTION

The eye is small, easy to reach and, at the same time, remarkably good at keeping drugs out. Topical instillation is still the default route for treating anterior segment disease, yet reflex tearing, blinking, nasolacrimal drainage and a tightly sealed corneal epithelium clear most of an instilled dose before it can act [11].

A commercial dropper delivers roughly 35–50 µL, while the conjunctival sac can hold only about 30 µL and the resident tear volume is close to 7–9 µL [22]. The excess overflows almost at once, and typically less than 5% of the applied dose reaches the aqueous humour [11]. Ointments stay longer, but they blur vision and are poorly accepted during the day.

For acute, self-limiting conditions, inefficiency is tolerable. For fungal keratitis, it is not. Corneal fungal infections often demand hourly dosing in the first days, followed by weeks of tapering therapy [21]. Missed doses mean sub-therapeutic stromal drug levels, a slower response and, potentially, perforation or loss of the eye.

Ocular inserts are sterile, thin, solid or semi-solid devices placed in the conjunctival sac or on the ocular surface to release drug over an extended period [18][29]. When built from mucoadhesive biopolymers such as chitosan, sodium alginate, hyaluronic acid or cellulose ethers, they can anchor to the mucin layer of the tear film and dissolve or erode once their job is done [14][20]. Some, chitosan in particular, have antimicrobial and permeation-enhancing activity of their own [4][28], and an impermeable backing layer can, at least in principle, direct release toward the cornea.

This review brings together the evidence relevant to mucoadhesive ocular inserts for fungal keratitis, with fluconazole as the model drug, and closes with the research gaps that still stand between laboratory prototypes and clinical use.

2. OCULAR ANATOMY AND PHYSIOLOGICAL BARRIERS TO DRUG DELIVERY

The cornea is a transparent, avascular tissue about 0.5 mm thick at its centre, made up of the epithelium, Bowman's layer, the stroma, Descemet's membrane and the endothelium [7]. Tight junctions between the superficial epithelial cells make the epithelium the principal barrier to hydrophilic and large molecules [27]. The stroma, roughly 90% of corneal thickness, welcomes hydrophilic solutes but slows lipophilic ones [7].

The tear film is traditionally described as an outer lipid layer, a middle aqueous layer and an inner mucin layer; membrane-associated mucins (MUC1, MUC4 and MUC16) coat the epithelial surface, while goblet cells secrete the gel-forming mucin MUC5AC [13]. This mucin layer is the very surface a mucoadhesive insert must grip. Normal tear turnover is about 1 µL/min, roughly 16% of tear volume per minute [22].

The combined effect of drop overflow, reflex tearing, blinking and drainage is precorneal loss, the single largest reason for poor topical bioavailability [11]. Figure 1 shows how little of the original dose ends up where it is needed.

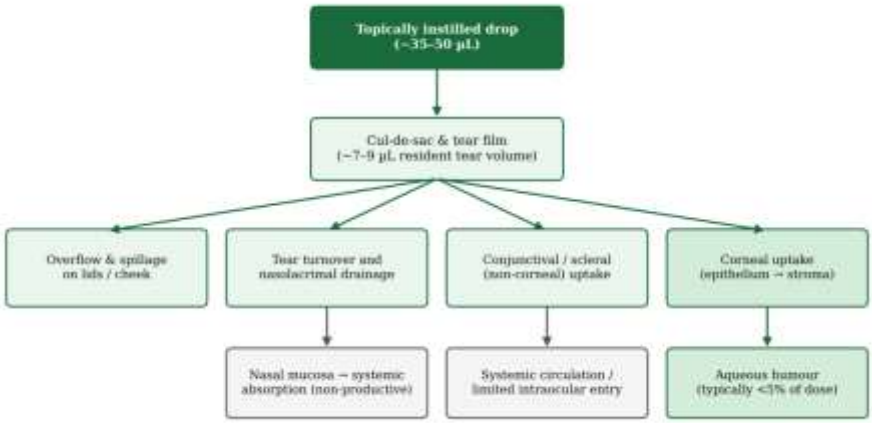


Figure 1. *Fate of a topically instilled ophthalmic drop, showing precorneal loss pathways and the small fraction that reaches the aqueous humour.[11][22]*

Once a drug reaches the corneal surface, the lipophilic epithelium and the hydrophilic stroma impose opposite demands, so a drug that partitions easily into the epithelium may stall in the stroma, and a highly water-soluble drug may never cross the epithelium efficiently [27]. Corneal penetration follows a parabolic relationship with lipophilicity, with an optimum log P of roughly 2–3 [30].

3. OCULAR FUNGAL INFECTIONS AND THE THERAPEUTIC ROLE OF FLUCONAZOLE

Fungal keratitis, or keratomycosis, is a suppurative corneal infection caused by filamentous fungi or yeasts, with an estimated 1.05 to 1.48 million cases a year, mostly in Asia and Africa, and a substantial proportion of affected eyes ending in blindness or loss of the eye [5]. Corneal trauma with vegetative matter is the classic route, so agricultural workers are especially at risk [21].

Filamentous fungi dominate in warm climates; *Fusarium* and *Aspergillus* species are the most frequently isolated genera. Yeasts, mainly *Candida* species, are more common in temperate regions and in eyes with pre-existing surface disease, immunosuppression or long-term steroid exposure. Diagnosis depends on corneal scraping with microscopy and culture [21].

Natamycin 5% suspension remains the first-line topical agent for filamentous keratitis. In the Mycotic Ulcer Treatment Trial I, natamycin gave better visual outcomes than topical voriconazole, especially for *Fusarium* ulcers [26]. Amphotericin B (0.15–0.3%) is commonly preferred for yeast keratitis, and azoles, including voriconazole, econazole, itraconazole and fluconazole, are used topically, orally or by intrastromal or subconjunctival injection depending on severity [16].

Every one of these options shares the same delivery bottleneck: natamycin penetrates intact epithelium poorly, amphotericin B is unstable and irritating, and most azoles must be compounded from systemic preparations [16].

Fluconazole is a synthetic bis-triazole antifungal. It inhibits fungal cytochrome P450-dependent lanosterol 14α-demethylase (CYP51, encoded by *ERG11*), blocking the conversion of lanosterol to ergosterol [12]. The effect is mainly fungistatic.

Its spectrum covers *Candida albicans*, most other *Candida* species and *Cryptococcus neoformans*, while activity against filamentous fungi such as *Fusarium* and *Aspergillus* is weak and inconsistent [12][16]. A fluconazole insert is therefore most defensible for yeast keratitis, or as an adjunct, rather than as a replacement for natamycin in filamentous disease.

Fluconazole is a white crystalline powder with a molecular weight of 306.27 g/mol, relatively hydrophilic for an azole (log P about 0.4–0.5) and essentially un-ionized at tear pH [6][25]. Yee and co-workers showed measurable corneal and aqueous humour levels after topical fluconazole in rabbits [35]. Table 1 links these properties to their consequences for ocular delivery.

Table 1. Physicochemical and Biopharmaceutical Profile of Fluconazole and Its Relevance to Ocular Delivery

Property	Reported value	Relevance to ocular delivery
Molecular weight	306.27 g/mol [25]	Well below 500 Da; small enough for paracellular and transcellular corneal transport
Aqueous solubility	Slightly soluble; markedly higher than most azoles [6]	Easy loading into hydrophilic biopolymer matrices; risk of initial burst release
Lipophilicity (log P)	About 0.4–0.5 [25]	Below the corneal optimum (log P 2–3), so epithelial partitioning is modest [30]
Ionization (pKa)	About 2 (weak base) [6]	Essentially un-ionized at tear pH 7.4; permeation is not pH-limited in the tear range
Plasma protein binding	About 11–12% [6]	Low binding favours free drug in ocular fluids and tissues
Elimination half-life (oral)	About 30 h [6]	Long systemic half-life; topical route still needed for high corneal levels
Antifungal spectrum	*Candida* spp., *Cryptococcus*; weak	Best suited to yeast keratitis or adjunct



Property	Reported value	Relevance to ocular delivery
	against *Fusarium* and *Aspergillus* [12]	therapy
Ocular penetration	Measurable corneal and aqueous humour levels after topical dosing in rabbits [35]	Supports topical use; prolonged contact should increase tissue exposure

Topical fluconazole is usually used as a 0.2–0.3% solution prepared from the intravenous formulation [16]; it is cleared within minutes, and with a log P below the corneal optimum it crosses the intact epithelium less readily than more lipophilic azoles [30]. This explains the steady stream of fluconazole carrier systems: niosomal gels [10], chitin nanogels [23], nanoparticles in in situ or mucoadhesive gels [2][8], dissolving microneedles [32] and freeze-dried chitosan inserts [34]. Most improved retention or permeation; few addressed directionality.

4. OCULAR INSERTS AS ADVANCED DRUG DELIVERY SYSTEMS

Ocular inserts are sterile, thin, drug-impregnated solid or semi-solid devices placed in the cul-de-sac or on the conjunctiva or cornea, classified as insoluble, soluble or bioerodible and by diffusion-, osmosis- or erosion-controlled release [18][29].

Early commercial devices such as Ocusert, a pilocarpine reservoir, and Lacrisert, a soluble hydroxypropyl cellulose rod, showed that technical performance alone does not guarantee acceptance [29].

Insoluble inserts offer precise, often zero-order release but must be removed after use [18]; soluble inserts swell and dissolve, with faster and more variable release [29]; bioerodible inserts degrade by hydrolysis or enzymatic cleavage [3]. For fungal keratitis, soluble or bioerodible mucoadhesive inserts are the more practical choice.

The arguments for inserts are well established: longer precorneal residence, accurate dosing, reduced systemic absorption, lower dosing frequency, no need for preservatives and better stability [18][29]. Each advantage carries a cost, however; inserts take more effort to manufacture, are harder to sterilize and may be felt as a foreign body. These trade-offs are compared in Table 2.

Drug-eluting contact lenses sit directly over the cornea, but a lens on an ulcerated, infected cornea is generally undesirable, and in situ gels are still diluted and drained; thin films overlap considerably with inserts [15].

Table 2. Comparative Analysis of Ocular Drug Delivery Systems for Anterior Segment Therapy

Delivery system	Precorneal residence	Advantages	Limitations
Eye drops (solutions/suspensions)	Minutes	Simple, cheap, easy self-administration, flexible dosing	Rapid drainage, <5% bioavailability, pulsatile levels, frequent dosing [11]
Ophthalmic ointments	Longer than drops	Prolonged contact; useful at bedtime	Blurred vision, greasy feel, poor daytime acceptance, dosing imprecision
In situ gels	Moderate	Instilled as liquid, gels on the eye (pH, temperature or ions)	Still diluted and drained; may blur vision; gel strength varies with tear conditions
Ocular films	Hours (polymer-dependent)	Thin, flexible, precise dose; can be mucoadhesive [15]	Handling of very thin films; variable dissolution; sterilization needed



Delivery system	Precorneal residence	Advantages	Limitations
Ocular inserts (soluble / bioerodible / insoluble)	Hours to days	Sustained, accurate dosing; fewer administrations; preservative-free [18][29]	Foreign-body sensation, expulsion, insertion difficulty; insoluble types need removal
Drug-eluting contact lenses	Hours to days	Drug delivered into slow-turnover post-lens tear film	Burst release, altered lens properties, undesirable on infected or ulcerated cornea

Foreign-body sensation remains the most cited barrier to insert acceptance; inserts can also be expelled during sleep or vigorous blinking. Mucoadhesive biopolymers soften quickly after hydration, which improves comfort, and they hold the insert in place, which reduces expulsion [20].

5. BIOPOLYMERS IN MUCOADHESIVE OCULAR INSERT FORMULATION

Biopolymers used in ocular inserts may be cationic (chitosan), anionic (alginate, hyaluronic acid, sodium carboxymethyl cellulose) or non-ionic (hydroxypropyl methylcellulose, hydroxypropyl cellulose, pullulan) [20]. Because ocular mucins carry negatively charged sialic acid and sulfate groups, cationic polymers can bind electrostatically, whereas anionic and non-ionic polymers rely mainly on hydrogen bonding and chain entanglement [31].

Chitosan, a cationic copolymer of glucosamine and N-acetylglucosamine (amino pKa about 6.5), binds negatively charged ocular mucins, transiently opens epithelial tight junctions [4] and has intrinsic antimicrobial and antifungal activity [28]; in rabbits it was well tolerated and prolonged precorneal retention [9].

Teba et al. produced freeze-dried fibrous chitosan inserts of fluconazole that released drug over 12 h and raised aqueous humour exposure about nine-fold in rabbits compared with a fluconazole solution [34]. Chitosan's drawbacks are poor solubility at neutral pH, batch-to-batch variability and brittle films unless plasticized [4].

Alginate is an anionic polysaccharide made of β-D-mannuronic and α-L-guluronic acid blocks; divalent cations such as calcium crosslink the guluronic blocks to form "egg-box" gels [19]. In brimonidine inserts, low-molecular-weight sodium alginate gave the most sustained release among several bioadhesive bases tested [3].

Hyaluronic acid (HA) is a viscoelastic, mucoadhesive glycosaminoglycan familiar from artificial tears; on its own it forms soft, rapidly dissolving films, so it is usually blended or crosslinked when used in inserts [14].

Cellulose ethers are the workhorses of ocular film formulation. Hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) form flexible, transparent films and swell into viscous gels; HPC is the sole component of Lacrisert [29]. Ethyl cellulose, by contrast, is water-insoluble, which makes it the most common choice for drug-impermeable backing layers and rate-controlling coatings [3][33].

Rarely does a single polymer meet every requirement, so blends such as chitosan with HPMC or polyvinyl alcohol, or alginate with chitosan, are common [3], and thiolated polymers (thiomers) show markedly stronger mucoadhesion than their parent polymers [4].

Polymer selection for a fungal keratitis insert should weigh ocular tolerability, mucoadhesive strength, film-forming ability, compatibility with fluconazole, a predictable swelling and release profile, and the ability to survive sterilization [20]. Table 3 compares the main candidates.

Table 3. Comparison of Biopolymers Used in Mucoadhesive Ocular Inserts

Biopolymer	Nature / charge	Advantages	Limitations
Chitosan	Polysaccharide; cationic (amino pKa about 6.5)	Strong mucoadhesion, tight-junction opening, intrinsic antimicrobial activity, good ocular tolerance [4][9][28]	Poorly soluble at neutral pH; batch variability; brittle films without plasticizer [4]
Sodium alginate	Polysaccharide; anionic	Ion-triggered gelation; moderate mucoadhesion; forms complexes with chitosan [19]	Rapid dissolution unless crosslinked; ionic sensitivity; source-dependent composition
Hyaluronic acid	Glycosaminoglycan; anionic	Endogenous, viscoelastic, mucoadhesive, soothing to ocular surface [14]	Soft, fast-dissolving films; costly; often needs blending or crosslinking
Cellulose derivatives (HPMC, HPC, NaCMC)	Semi-synthetic; non-ionic (HPMC, HPC) or anionic (NaCMC)	Excellent film formers; controlled swelling; HPC used in Lacrisert [29]	Weaker mucoadhesion than chitosan; release depends on viscosity grade
Ethyl cellulose	Semi-synthetic; non-ionic, water-insoluble	Drug-impermeable backing layer or rate-controlling coat [3][33]	Not mucoadhesive; adds stiffness; possible delamination
Gelatin	Protein; amphoteric	Biocompatible, biodegradable, tunable by crosslinking	Animal origin; limited mucoadhesion; crosslinker toxicity concerns
Pullulan	Fungal polysaccharide; neutral	Clear, strong, highly soluble films	Weak mucoadhesion; dissolves quickly; usually a partner polymer
Thiolated polymers (thiomers)	Modified polymers; charge of parent	Disulfide bonding with mucin; much stronger adhesion [4]	Oxidation during storage; regulatory novelty

6. MUCOADHESION MECHANISMS AND STRATEGIES FOR PROLONGED OCULAR RESIDENCE

Mucoadhesion is the attachment of a material to a mucus-covered surface. Several complementary theories describe it: wetting, diffusion (interpenetration), electronic, adsorption and fracture theories [31]. In practice, adhesion of a dry insert to the eye follows a sequence of contact, hydration, interpenetration and bonding (Figure 2).



Figure 2. *Sequential stages of mucoadhesion between a polymeric ocular insert and the ocular mucin layer.*

Adhesion begins when a dry insert spreads across the tear film and takes up water, which relaxes the polymer chains and exposes adhesive functional groups [31]. Polymer chains and mucin glycoproteins then entangle, hydroxyl, carboxyl and amino groups form hydrogen bonds with mucin sugars, and cationic chitosan binds the negatively charged sialic acid residues of mucin electrostatically [4][31]; thiomers go further, forming covalent disulfide bridges [4].

7. UNIDIRECTIONAL DRUG RELEASE AND TRANSCORNEAL DELIVERY STRATEGIES

A conventional monolayer insert releases drug from every exposed surface, so the face exposed to the tear film releases drug into fluid that is drained away. In unidirectional delivery, a drug-loaded mucoadhesive layer faces the target tissue and an impermeable backing layer covers the other side, so release, at least ideally, occurs only toward the cornea (Figure 3). The idea comes largely from buccal delivery [24].

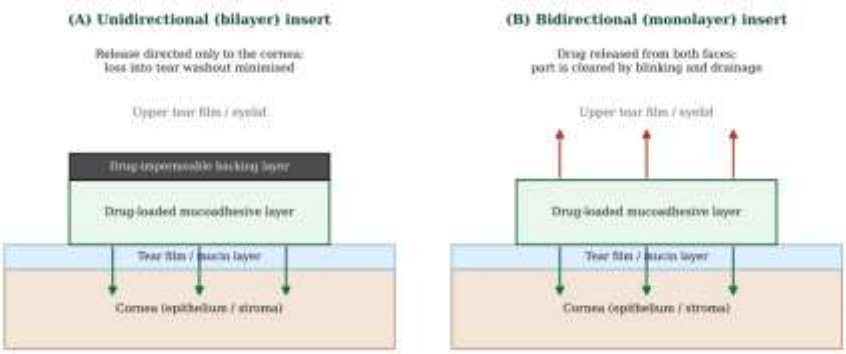


Figure 3. *Schematic comparison of (A) a unidirectional bilayer insert with a drug-impermeable backing layer and (B) a conventional bidirectional monolayer insert.*

A backing layer must be insoluble in tear fluid, impermeable to the drug, flexible and firmly bonded to the drug layer; ethyl cellulose is the most common choice [24][33]. Aburahma and Mahmoud found that brimonidine alginate–PVP inserts coated with ethyl cellulose or Eudragit RSPO on one side produced a greater intraocular pressure reduction in rabbits than uncoated or dual-coated inserts [3], and Tanwar et al. obtained close to zero-order release of ofloxacin over 24 h with ethyl cellulose and Eudragit rate-controlling membranes [33].

Release from a hydrophilic insert combines swelling, diffusion through the gel layer and erosion. In the Korsmeyer–Peppas model for thin films, a release exponent near 0.5 indicates Fickian diffusion, 0.5–1.0 anomalous transport and near 1.0 case II, relaxation-controlled release [17]. In Teba's chitosan inserts, fluconazole release fitted the Higuchi model with a Fickian mechanism [34].

Release and permeation depend on drug solubility and loading, polymer type and ratio, insert thickness, degree of crosslinking, plasticizer content and the integrity of the backing layer. Fluconazole's good water solubility simplifies loading but also favours a burst effect; Teba et al. reported an initial burst of about 16% before sustained release [34].

A unidirectional system confines release to the tissue-contacting face, so less drug is needed to reach the same tissue concentration [24]. The trade-offs are slower overall release, added thickness and stiffness, possible delamination of the two layers on hydration, and the need to place the insert with the correct face toward the cornea [18].

8. FORMULATION DEVELOPMENT AND OPTIMIZATION

Formulation begins with a defined target product profile: indication (here, yeast keratitis), dose, release duration and insert dimensions. Plasticizers such as glycerol, propylene glycol or polyethylene glycol are added to reduce brittleness [15].

Ocular inserts can be prepared by solvent casting, hot-melt extrusion, compression, freeze-drying, electrospinning and three-dimensional printing [15]. Solvent casting is by far the most common; freeze-drying produces porous, rapidly hydrating matrices and was used by Teba et al. for fibrous chitosan inserts of fluconazole, whose compatibility was confirmed by FTIR and thermal analysis [34].

In solvent casting, the polymer, plasticizer and drug are dissolved in a suitable solvent, degassed, poured into a level mould and dried. For a bilayer insert, the backing layer is usually cast first and the drug layer cast over it, or the two layers are laminated (Figure 4) [24].



Figure 4. *General workflow for preparing mucoadhesive ocular inserts by solvent casting, including the optional backing layer for unidirectional designs.*

The main formulation variables are polymer ratio, plasticizer level, drug loading and insert thickness, and statistical designs help map their interactions; a simplex-lattice design was used, for instance, to optimize fluconazole microemulsion-loaded microneedles [32]. Table 4 summarizes published antifungal ocular delivery work.

Table 4. Published Studies on Antifungal Ocular Drug Delivery Systems

Drug	Polymer / carrier	Formulation	Evaluation methods	Key findings	Limitations
Fluconazole [34]	Chitosan (0.02–1% w/v)	Freeze-dried fibrous ocular insert	SEM, FTIR, DSC, swelling, release, bovine corneal permeation, MTT, Draize, rabbit PK	Sustained release over 12 h; about 9.3-fold higher aqueous humour AUC and 3.3-fold higher Cmax vs solution	Monolayer (bidirectional); healthy eyes; no infection model
Fluconazole [10]	Span 60/80–cholesterol niosomes in poloxamer 407 or chitosan gel	Niosomal gel	Entrapment, size, release, goat corneal permeation, antifungal assay	Poloxamer gel released and permeated more than chitosan gel; strong antifungal activity	Semi-solid gel; residence still limited by drainage
Fluconazole [2]	Pluronic F-127 stabilized nanoparticles in sodium alginate or Carbopol gel	Nanoparticle-loaded gel	Size, zeta, DSC, XRPD, goat corneal permeation, rabbit PK	About 1.4-fold higher aqueous humour AUC vs plain gel	Modest PK gain; no efficacy model
Fluconazole [8]	HP-β-CD complex in Eudragit RS100 nanoparticles or chitosan-coated niosomes;	Thermosensitive in situ gel	Release, corneal flux, antifungal activity in rabbits, Draize, histology	About 2.5–3.4-fold higher flux and longer release than drug solution	Complex multi-step system; scale-up difficult



Drug	Polymer / carrier	Formulation	Evaluation methods	Key findings	Limitations
	poloxamer–HPMC–chitosan gel				
Fluconazole [23]	Chitin	Nanogels	DLS, zeta, SEM, FTIR, cytocompatibility, porcine corneal penetration	Controlled release; deeper corneal penetration without damage	Ex vivo only
Fluconazole [32]	Chitosan/PVA shell with microemulsion core	Two-layered dissolving microneedles	Mechanical tests, insertion, tissue delivery, stability, antifungal assay	Higher ocular tissue delivery; stable for three months	Minimally invasive; patient acceptance untested
Natamycin [1]	Solid lipid nanoparticles in Carbopol 940/HPMC gel	Mucoadhesive SLN gel	Mucoadhesion, release, *Candida* keratitis model in rabbits, histology	Better efficacy and histopathology than marketed product	Semi-solid; dosing still required

9. CHARACTERIZATION AND EVALUATION OF MUCOADHESIVE OCULAR INSERTS

Inserts are checked for appearance, thickness and weight uniformity, drug content, surface pH, swelling, folding endurance, mucoadhesive strength, in vitro release, ex vivo corneal permeation, irritation and sterility [24][33] (Table 5). Teba's chitosan insert, for example, showed an entrapment efficiency of about 88% and fibroblast viability above 80% [34]. For bilayer inserts, release should also be tested from the backing side alone.

Table 5. Techniques for Evaluating Mucoadhesive Ocular Inserts

Test method	Purpose	Relevant parameters	Interpretation
Visual inspection; micrometer or screw gauge; analytical balance	Physical uniformity	Appearance, thickness at several points, weight variation [33]	Low SD indicates uniform casting and dose
UV spectrophotometry or HPLC assay	Drug content and uniformity	% drug content per insert; entrapment efficiency where carriers are used	Content close to label claim with low variability
Folding endurance; tensile testing (texture analyzer)	Mechanical robustness	Number of folds, tensile strength, elongation at break [15][24]	Flexible yet strong films resist tearing during insertion
Detachment force (modified balance or texture analyzer)	Mucoadhesive strength	Force and work of adhesion on mucosa or mucin	Higher force suggests longer residence, within comfort limits
Vial, Franz cell or flow-	In vitro release	Cumulative release in	Model and n value



Test method	Purpose	Relevant parameters	Interpretation
through release study		simulated tear fluid; kinetic model fitting [17]	indicate diffusion, anomalous or relaxation control
Ex vivo corneal permeation (goat, bovine or porcine cornea)	Transcorneal transport	Flux, permeability coefficient, lag time, corneal hydration [10][34]	Higher flux vs solution indicates enhanced permeation
Draize test, HET-CAM, BCOP; MTT assay; histology	Irritation and biocompatibility	Irritation scores, cell viability, tissue changes	Non-irritant, >80% viability supports ocular safety
Sterility testing; ICH stability studies	Sterility and shelf life	Microbial growth; changes in content, release and mechanics over time	No growth and stable attributes support product viability

10. PRECLINICAL AND TRANSLATIONAL ASSESSMENT

Teba's chitosan insert outperformed a fluconazole solution against *Candida albicans* [34], and both poloxamer and chitosan niosomal gels showed strong antifungal activity [10]. In rabbits, fluconazole nanoparticle gels increased aqueous humour AUC about 1.4-fold [2], cyclodextrin-based nanoparticles and niosomes in an in situ gel produced higher corneal flux and a stronger antifungal effect than a drug solution [8], and a single chitosan insert kept aqueous humour levels above the MIC with roughly 3.3-fold higher Cmax and 9.3-fold higher AUC than a fluconazole solution [34].

Efficacy studies in induced keratitis models are less common; a natamycin solid lipid nanoparticle mucoadhesive gel outperformed the marketed product in rabbits with *Candida* keratitis [1], but efficacy data for fluconazole inserts in an infected eye are very limited. Most experiments also use healthy rabbit eyes [21], and clinical trials remain dominated by drug comparisons such as natamycin versus voriconazole [26].

11. CRITICAL CHALLENGES AND RESEARCH GAPS

The strongest adhesive is not the best insert: excessive adhesion can damage the epithelium on removal, while weak adhesion leads to expulsion [20]. Directional release is easy to draw and difficult to prove, since few ocular studies have verified backing-layer impermeability or layer adhesion after hydration [3][33]. Natural polymers vary with source and processing [4], sterilization and stability are rarely reported, and laboratory casting offers no route to manufacture. Despite decades of research, very few ocular inserts have reached the market, and none is approved for fungal keratitis [29]. These gaps, and possible ways to close them, are summarized in Table 6.

Table 6. Research Gaps and Future Directions for Mucoadhesive Antifungal Ocular Inserts

Current limitation	Impact	Proposed solution
Fluconazole has weak activity against filamentous fungi	Limits use to yeast keratitis; risk of treatment failure in *Fusarium* or *Aspergillus* cases	Position inserts for *Candida* keratitis or adjunct use; explore co-loading with natamycin or voriconazole
Few ocular studies verify directional release	Benefit of backing layers remains largely theoretical	Test release from each face; confirm backing impermeability; report layer adhesion after hydration



Current limitation	Impact	Proposed solution
Balance of mucoadhesion and comfort is rarely measured	Poor patient acceptance, expulsion or epithelial damage	Use soft, rapidly hydrating layers; thin, rounded designs; collect patient-reported comfort data
Healthy-eye animal models dominate	Retention and PK may not reflect inflamed, ulcerated cornea	Use standardized infected keratitis models; measure stromal drug levels
Variability of natural polymers	Inconsistent adhesion, release and antimicrobial effect	Specify molecular weight, degree of deacetylation and purity; apply QbD and design-space controls
Sterilization and stability rarely reported	Products may not survive manufacture or storage	Validate gamma, ethylene oxide or aseptic processing; run ICH stability studies
Laboratory-scale casting and cutting	Poor reproducibility; no route to manufacture	Adopt continuous casting, lamination or 3D printing; borrow from oral film manufacturing
Absence of clinical studies	No evidence of benefit in patients	Plan early-phase trials comparing inserts with standard drops in culture-proven yeast keratitis

12. CONCLUSION AND FUTURE PERSPECTIVES

Fungal keratitis is a delivery problem as much as a drug problem, and mucoadhesive ocular inserts offer a rational alternative to hourly drops. Fluconazole fits this platform well, though not universally: it is easy to formulate, but its weak activity against filamentous fungi limits its use mainly to yeast keratitis or adjunctive therapy. Preclinical fluconazole nanocarriers, gels and freeze-dried chitosan inserts have shown longer release, better corneal permeation and higher aqueous humour exposure than conventional solutions.

Unidirectional design is the logical next step, but for ocular antifungal inserts it is still largely untested. Future work should combine mucoadhesive layers with validated backing layers, test release from each face, measure stromal drug levels, use infected animal models and collect patient-reported comfort data, so that unidirectional inserts can move from a sound idea to a usable treatment.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

[Karishma Nishad]: Conceptualization, literature search, data extraction, preparation of tables and figures, and original draft preparation.

[Deepak kumar singh]: Critical review of content, interpretation of the literature, and editing of the manuscript.

[Deepak kumar singh]: Supervision, scientific guidance, final review, and approval of the manuscript for submission.

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