Therapeutic Contact Lenses for Intraocular Drug Administration: Innovations and Applications in Treating Fungal Keratitis

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ABSTRACT

This review examines the advancements in ocular medication administration, focusing on therapeutic contact lenses (TCLs) as a novel approach for treating fungal keratitis. Traditional eye Drops' bioavailability is poor due to various anatomical and physiological barriers, necessitating frequent administration and leading to poor patient compliance. TCLs offer a promising alternative, providing extended drug release, improved bioavailability, and enhanced patient comfort. This review explores different antifungal drugs, innovative methods for drug incorporation into TCLs, and their therapeutic efficacy. The potential of TCLs to revolutionize ocular drug delivery and improve treatment outcomes for fungal keratitis is discussed.

1. Introduction

Technology Among the most interesting aspects of localized drug delivery is ocular drug delivery. The eye is the chosen pathway for treating ocular illnesses because it is easily accessible by the patient. It's commonly used to treat infections, inflammations, dry eye, and cataracts in the anterior portion of the eye (1). Some posterior illnesses, such as glaucoma, can be treated with a topical treatment. However, due of the numerous barriers that reduce the efficacy of medications employed, it was and remains one of the most difficult challenges for pharmaceutical researchers. (2,3). The majority of dosage forms currently used in the clinic are applied directly used topically as eye drops, suspensions, gels, and ointments, with eye drops accounting for around 90% of all dosage forms (4). Due to several anatomical, physiological, and biological barriers, only around 5-10% of administered eye drops reach the needed site of action figure 1 (5). Eye drops must be given frequently to compensate for the low bioavailability, which can lead to inadequate patient adherence, particularly in the case of persistent ocular conditions as dry eye and glaucoma. Furthermore, between 11.3 percent and 60.6 percent of Patients don't always apply in precisely single drop while applying eye drops, and between 18.2 percent and 80 percent of the patients run the risk of touching their eye or face and contaminating their eye drop bottle with facial germs.

Because of this, most patients struggle to apply the recommended eye drop procedure, which may have an impact on the course of their treatment. This can be one of the reason for unexpected disobedience (6). The first line of defense in the eye is pre-corneal factors, which limits the absorption of ocular drugs applied topically. The reflexive blinking, a high tear turnover rate, and lacrimal drainage of the solution are among them. An applied eye drop can be conducted in the dead end of the eye for about thirty minutes. However, most of this is gone within fifteen to thirty seconds of the drops being applied. In order to bring about changes, drug delivery devices that can improve It is necessary to develop formulation retention at the administrative location. (7)

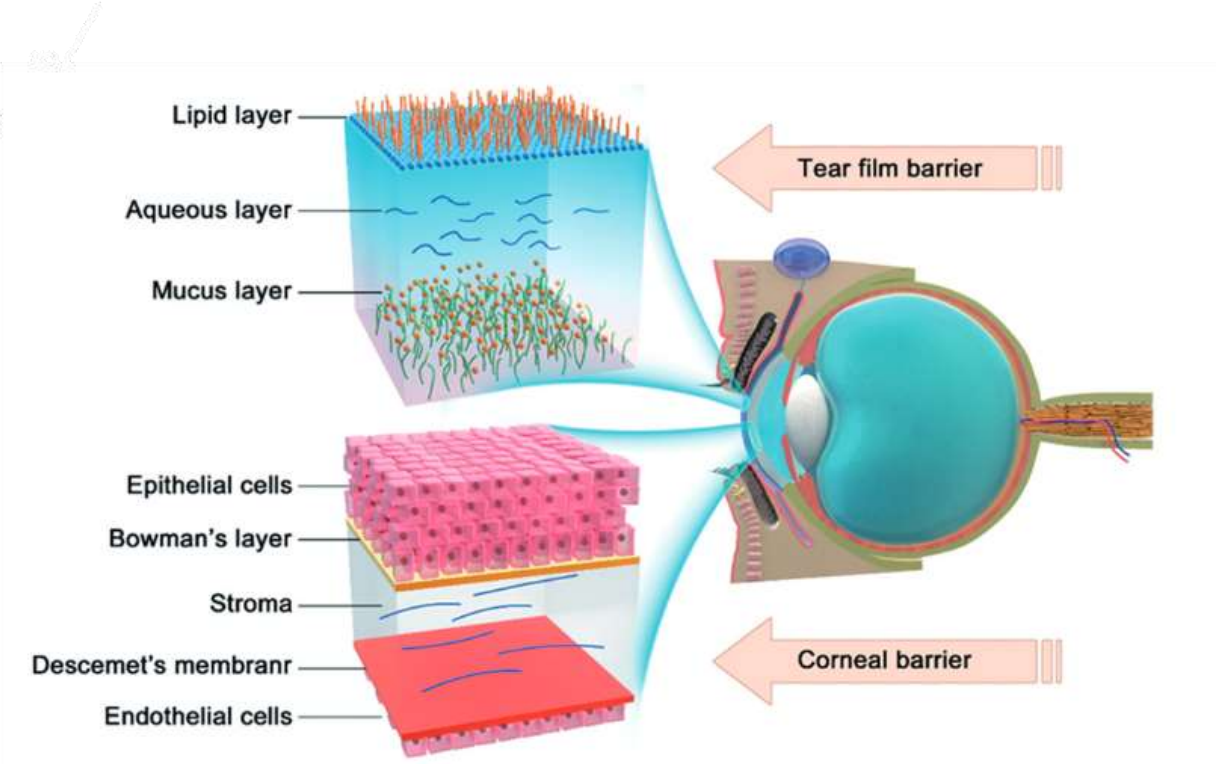

Figure 1: Barriers to ocular drug delivery. The cornea is considered as the main barrier for topically applied medication (8).

Therapeutic contact lenses:

Therapeutic contact lenses (CLs) are transparent, hemispherical, plastic thin lens wear on cornea either to protect the eyes or enhance eyesight. Due to their unique characteristics such as prolonged wear, quick cessation of medication through removing the lens, & high bioavailability (>fifty percent). They are an alternative to glasses for correcting and improving eye vision and also used for aesthetics CLs have recently been employed for therapeutic purposes (9).

They are used to treat diseases such as myopia, hyperopia, astigmatism, and presbyopia.(10) They are highly compatible with ocular tissues due to their soft nature and the use of biocompatible polymers in their fabrication (11). In recent decades, scientists were interested in using CLs as drug delivery system in the eye through the development of therapeutic contact lenses (TCLs) (12). The released drug has a longer PCRT and an additional direct diffusion path to the ocular surface due to the lens's protection against lachrymal fluid exchange and blinking reflexes. 50% of the drug that enters the post-lens tear film after being removed from contact lenses is ocularly bioavailable and has a 30-minute residence period.

They may also be made to be comfortable and safe to wear for longer periods of time, allowing for longer treatment period. CLs, in general, enable for non-invasive medication delivery, are easy to use, and are affordable (13). CLs are classified into three types based on their composition: rigid (hard), soft and hybrid CLs (14).

1. **Rigid contact lens**: Rigid contact lenses (RCLs) were the first to be produced in the form of glass lenses with a range of designs for the treatment of astigmatism and corneal abnormalities. The first RCL was made of glass, and it was later replaced by poly methyl methacrylate (PMMA). PMMA had a 20-fold higher oxygen permeability than PMMA and could be manufactured using molding techniques(15).
2. **Soft contact lens:** Soft CLs were developed to overcome some of the problems associated with

RCLs, especially rigidity and water content. Soft CLs are hydrogel in nature and formulated by the crosslinking of water soluble polymers such as HEMA and N vinyl pyrrolidone (NVP), methacrylic acid (MAA), dimethacrylamide (DMA), acrylic acid (AA) and polyvinyl alcohol (PVA) (16). Hydrogel is combined with silicone rubber to allow extremely high oxygen permeability and still maintain the compatibility and flexibility of the lens. Although hydrogels are permeable to oxygen, their permeability is low(16).

3. **Hybrid contact lenses:** Hybrid contact lenses comprise an RGP core and soft edges. They are intended to be applied to the sclera, ascending the cornea without making any point of apex contact. They may increase vision extremely efficiently because to their RGP center and give improved lens centration and comfort owing to their soft edges. They have been on the market since the 1980s and are a viable alternative to RGPs, especially in uneven corneas. (17, 18).

Table 1: Properties of Various Contact Lens Materials (19)

Material	Oxygen Permeability (Dk/t)	Water Content (wt %)	Modulus (MPa)	Wear Time (days) *
PMMA	0	0	1000	<1
PMMA-silicone	15	0		
Silicone-HEMA (rigid)	10–100	0	10	
HEMA hydrogel	10–50	30–80	0.2–2	1–7
HEMA-NVP				
HEMA-MMA				
Silicone (PDMS) hydrogel	60–200	20–55	0.2–2	~7–28
TRIS-DMA				
PDMS-HEMA				
PVA	10–30	60–70		<1

Innovative techniques for making medication-loaded contact lenses:

The simplest approach available for creating drug-loaded contact lenses is the immersion method. However, this approach has drawbacks such as limited drug loading and rapid release speed due to the impact of the contact lens's water content on the drug's molecular solubility (20). Numerous advancements in the lens manufacturing procedure, including improving the loading capacity of the drug & drug release prolongation, several techniques have been used, including polymer nanoparticles, vitamin E barrier, molecular imprinting, ionic interactions, drug polymer film/coating, supercritical fluid technologies, and others (Table 2) (21, 22, 23).

Imprinting of molecules:

Using a template-mediated polymerization mechanism, molecular imprinting is a polymer synthesis technique that creates macromolecular networks with specific affinities, capabilities, and selectivities for template molecules (24). The drug and functional monomer are first polymerized, and the drug is subsequently removed, leaving the polymer network with a cavity for high-affinity drug identification. Drugs have the ability to engage with high-affinity cavities during reloading in

order to interact with efficient groups in the polymer network and raise partition coefficient.

Nanoparticles of polymers:

This procedure involves dispersing colloidal nanoparticles (nanoparticles, polymer nanoparticles, etc.) carrying medications into the polymerization solution containing monomers that have unreacted in order to manufacture contact lenses (25). The molecules of drugs often have restricted diffusion and a long releasing period as they must diffuse from nanoparticles & pass across the matrix of the lens to reach the tear film (26). Drug-loaded nanoparticles can also increase the effectiveness of treatment by preventing drug breakdown by enzymes such as lysosomes and by removing medication interactions with polymer mixtures (25).

Vitamin E barrier:

By placing obstacles in the way of the medication's transport, the vitamin E barrier slows down the rate of drug delivery and lengthens its release period. Via several methods, vitamin E can prolong the duration of medication release. Drug molecules that are hydrophobic can dissolve at high concentrations, whereas hydrophilic drug molecules can be forced to diffuse out of the lens along complex routes (27). It is said that vitamin E preserves the lenses' ability to transmit visible light as well as additional characteristics.

Integration of vitamin E can increase the bioavailability of bimatoprost to more than 50% while having no effect on latanoprost transport (27). While contact lens was saturated in vitamin E solutions, Rad *et al.* observed that the water contented was dramatically decreased, the loading capacity of betamethasone was increased, & the rate of release was lowered. Furthermore, they discovered that the application of vitamin E loading solutions, at concentrations of 0.1 & 0.2 g/mL, would successfully extend the release time of cipro from 2 hrs (in a lens that was not loaded with vitamin E) to 14 to 17 and 30 to 33 days, respectively (28).

Furthermore, vitamin E's potent antioxidant qualities can shield the cornea from UV rays, increase the stability of combination medications, and stop the progression of diseases including cataracts and age-related macular degeneration. (29).

Ionic interactions:

Ocular medications are primarily charged in a physiological environment, so it is possible to exploit ionic interactions to boost the drug's binding to the substrate. Stronger adsorption may result from the ionic surfactants' hydrophobic interactions with gel polymers and the electrostatic contacts of medicines. Adsorption of ionic medicines onto polymers coated with surfactants can lower the pace of transport and extend the duration of release. When Torres-Luna et al. used a cationic surfactant in conjunction with the microemulsion technique to create contact lenses, they discovered that the release period could be extended by using microemulsions at low cetalkonium chloride weight percentage and a cationic surfactant. (30).

Table 2: Hydrogel Soft Contact Lenses That Have Received FDA Approval for Extended Wear.

Lens Brand	Material	Manufacturer
Kontour 55	Methafilcon A	Kontour Kontact
Soflens 38	Polymacon	Bausch & Lomb
Silsoft	Elastofilcon A	Bausch & Lomb

Acuvue-2	Etafilcon A	Vistakon
Softcon	Vifilcon A	Lombart
Preference	Tetrafilcon A	Cooper Vision
Fresh Look	Phemfilcon A	Alcon
Air Optix Aqua	Lotrafilcon B	Alcon
Acuvue Oasys	Senofilcon A	Vistakon
PureVision	Balafilcon A	Bausch & Lomb

Fungal keratitis:

Keratitis is an inflammatory disease of the eye that causes corneal opacity, redness, pain, and itching. Keratitis can be caused by bacteria, fungus, viruses, or protozoa. Keratitis can develop to sight-threatening consequences such as corneal scarring, perforation, endophthalmitis, and eventually blindness if left untreated. Keratitis affects approximately a million people worldwide each year. Keratitis affects almost 2 million persons in India each year (31). filamentous fungi (Fusarium and Aspergillus) &/or yeast (Candida); are the most prevalent fungi responsible for corneal attack that develops to fungal keratitis (FK). Excessive application of broad-spectrum antibiotics and steroids causes ocular damage, which disrupts the surface corneal microorganism balance, allowing pathogens to invade ocular tissue. Ocular injuries contaminated by soils and residues of plants (typically rich in Fusarium) is a supporting and causative factor for FK in farm situations, particularly in tropical and temperate regions.(32)

Antifungal drugs used to treat fungal keratitis:

For fungal keratitis, eye drops or topical ophthalmic solutions are the most commonly used treatment, only 15-27 percent of patients need an operation. Failures in topical antimycotic treatments can be associated with eye drop limitations. Low residence of the drug in ocular tissues reduce the period at which the drug in contact with ocular surfaces in therapeutic doses (33).

In many cases, cure remains difficult despite the emergence of new medicines. Antifungals have reduced efficacy compared to antibacterials due to their method of action (usually fungistatic, with dose dependent fungicidal action) (34). Moreover, many medicines have difficulty penetrating the epithelial of the cornea. Increased dosage levels and extended tissue duration of contact may overcome barrier effect. As a result, antifungal drops should often be administered every hour initially day and night by patients. The drop frequency is reduced if the treatment method is effective, but it persists for week-to-month periods. Causing poor compliance. A sustainable release system could improve compliance and treatment effectiveness for ophthalmic drugs, including antifungal products (33).

TCLs offer the solution to the problems associated with the use of antifungal medication by extending the release of the loaded drug, enhancing the amount of drug loaded and control the release of the drug to achieve constant dosage.

Ocular fungal infections can be treated with one of three kinds of antifungal medications:

1. Polyene (Natamycin):

Natamycin (NAT), is considered the first-line treatment for fungal keratitis, a strong, broad-spectrum antifungal medication which is effective & safe at low dosages. NAT is fungicidal & exert

a dose-dependent activity. The FDA has only approved NAT as a therapy for FK. The most effective treatment for filamentous FK, in accordance with the American Academy of Ophthalmology, is NAT. However, case management was challenging due to limited corneal penetration, necessitating a lengthy course of therapy (eye drops containing NAT 5 percent; every 1-2 hrs for 4-6 weeks).

2. Azole antifungal:

Azole antifungal medications are among the most extensively used antifungals, having effectiveness against a wide range of fungal infections and without the nephrotoxic side effects. There are two types of azoles that are available in the clinic: imidazoles (fluconazole, itraconazole, voriconazole, posaconazole, & isavuconazole) & triazoles (ketoconazole) (35).

3. Allylamines – terbinafine, naftifine:

As with azoles and polyenes, allylamines are not widely used in clinical practice. Terbinafine and naftifine, on the other hand have demonstrated efficacy against a variety of dermatophytes and yeast, and both are well tolerated with only mild side effects like burning or itching. (36).

Strategies to deliver antifungal drugs using TCLs:

There are many methods used to incorporate drugs into CLs. The main methods that were used to prepare antifungal CLs are:

1) Soaking method:

Earlier in the development process of TCLs the drug was incorporated through soaking method in which the dry lens is soaked in a drug solution. Results have shown that the ability of conventional contact lenses to become medication reservoir depends heavily on the thickness of the lens, the water content, drug-loading solution concentration, drug molecular weight, and time the lens remains in the soaking solution (37, 38).

Phan *et al.* did another study. This study examined the effectiveness of this delivery mechanism as well as the absorption & release of ocular antifungal medication Natamycin from the available commercially silicone hydrogel (SH) & conventional hydrogel (CH) contact lenses material. This study examined 5 commercial SH CLs (comfilcon A, galyfilcon A, senofilcon A, balafilcon A & lotrafilcon B) as well as 4 CH CLs (omafilcon A, polymacon, vifilcon A, & etafilcon A).

These lenses are incubated in Unisol 4 pH 7.4 at 32±1°C for 24 hours along with Natamycin solubilized in dimethyl sulfoxide (DMSO), & drug release was measured by UV-visible spectrophotometry at 305 nm. All CL materials showed a considerable absorption of Natamycin between 0 and 24 hours. However, regardless of composition, there was no discernible difference between any of the lenses material. All the SH materials and the CH material had a substantial variation in release. Natamycin release increased significantly in all CL materials until 1 hour, after which it plateaued. Overall, CH lenses released more Natamycin than SH lenses (39).

Another study looks at how 2 silicone hydrogel contact lens (CL) affected the growth of Candida albicans in an in vitro ocular condition after being soaked in either fluconazole (FL) or natamycin (NA). Three-dimensional printing molds were used to create eye-shaped replicas out of potato dextrose agar. The CLs of senofilcon A (SA) & lotrafilcon B (LB) are incubated with 2 mL of FL at 1 mg/mL or 2 mL of NA for a duration of 24 hours. To simulate a fungal infection, C. albicans was applied to the eye replicas. The eye models are fitted with the drug-soaked contact lenses.

The agar eyeballs from all experimental condition were withdrawn from the incubator & photographed at certain temporal intervals (t=1, 8, 16, 24, 48 hrs). Light microscopy was used to

examine yeast cells at one day and 2 days' time points. Except for the NA-SA and NA-LB conditions, all conditions showed significant growth at 24 and 48 hours. The morphology of the yeast cells in the FL-SA and SA conditions was identical to that of the control when viewed under the microscope at 24 and 48 hours (oval shaped). The NA-LB group had strong visible hyphae development while the LB group had little hyphae growth. The cells in the NA-SA, NA-LB, and FL-LB groups were considerably smaller than those in the control group. Even after 48 hours, C. albicans growth on the ocular models was restricted for NA-SA and NA-LB. The cell morphology differs considerably between each testing condition under the microscope, and is reliant on drug-lens combinations(40).

The most recent in vitro study looked at voriconazole topical medication administration both alone and in combination with diclofenac utilizing drug-loaded contact lenses.

In order to replicate in vivo conditions, the contact lenses were implanted on surgically removed pig eyes and maintained at 32 °C with constant irrigation using artificial tear fluid. To ascertain the dosage of medication administered to the corneas, HPLC analysis was employed.

The device was then examined for cytotoxicity as well as a scratch wound repopulation model employing resident cell types. Sustained drug delivery to the cornea was obtained, and the MIC for voriconazole against Acanthamoeba castellanii was reached both alone and in combination with diclofenac. The concentration of voriconazole in the cornea when CLs was used ranged between (38.5-77.6 μg/ml) through the time points while the eye drop was (27.8 and 37.4 μg/ml). At the medication dosages utilized, the results indicated satisfactory cell growth and wound repopulation, indicating that the system might be used to treat Acanthamoeba keratitis(41).

2) Loading the CL with Vitamin E

3) In order to control the diffusion of an active medication in a contact lens matrix, the method outlined here involves building diffusion barriers inside the lens. This forces a bioactive agent to diffuse out of the lens via a long, winding route, providing extended release.(42)

4) According to Cheng et al.'s research, the medication was soaked and loaded into the vitamin E-laden CL after the CL had been loaded with varying concentrations of vitamin E. For a 17% Vitamin E loading, fluconazole is released in 10 hours; for a 26%, 39%, and 66% loading, it is released in 24 hours; this represents a 6.2, 14, 55, and 142-fold increase in release length, respectively.(42)

5) CLs functionalized with Cyclodextrin:

In the nonappearance of particular mechanisms which permit drug molecules to interact, most hydrogels, including pHEMA hydrogels, exhibit restricted loading and poor drug release control. Co-polymerization of HEMA with monomers capable of forming particular ionic or hydrophobic contacts with drug molecules had been situated extensively investigated by way of a method to optimize the loading/release behavior of drug-loaded hydrogels. If the drug is poorly soluble in water, the concentration reached within the hydrogel will be low as well. To resolve these issues, we recently suggested post-functionalization of prepared hydrogels with pendant b-CDs. Because the CDs do not participate in or interfere with network creation, the approach allows the hydrogel's original characteristics to be preserved (43).

In a research, poly (hydroxyethyl methacrylate) (pHEMA) hydrogels were functionalized with pendant a-, b-, and c-cyclodextrins (CD) to improve biocompatibility and drug molecule hostability. The hydrogels were loaded with miconazole by immersing them in a drug solution and then autoclaving them. Functionalization with c-CD increased the network's affinity for the drug and resulted in the maximum quantity loaded (up to 170 mg/g). For several days, sustained delivery was

seen. In an in vitro microbiological test, several miconazole-loaded hydrogels totally inhibited Candida albicans biofilm development (43).

6) PLGA film encapsulated in pHEMA CLs

In one investigation, a contact lens made of a drug-loaded polymer film encapsulated within pHEMA was used. Over at least 30 days, a near zero-order release of quite significant amounts of drug was obtained using a flat prototype contact lens. An investigation describes the formulation and characterisation of a contact lens designed to deliver an antifungal drug, econazole, over an extended period of time. 200 mg of econazole incorporated into100 mg of PLGA and ethyl acetate, formed into three different surface area sizes .It has been demonstrated to be useful in treating fungal keratitis. The econazole-polymer films enclosed inside the contact lenses were created using poly(lactic-co-glycolic) acid (PLGA). Cls contained 16 mg of the drug killed 100% fungi effectively for 21 days in the release medium(44).

7) Molecular Imprinting Technique

Among the most interesting new methods for managing drug loading and distribution through CLs is MI. the concept was first introduced in 1972 and its fundamental feature is the use of the drug with the monomer mixture during polymerization process to create macromolecular memory sites (cavities). To generate stable and distinct template binding sites, monomers are spatially arranged and crosslinked around the template molecule (the medication) throughout the imprinting process (45). Following polymerization, the medication is rinsed, resulting in cavities that resemble the medication Figure 2. These locations will decrease the release of the medication from the hydrogel CL matrix while also increasing the selectivity and affinity of the CLs to the drug during the loading process.

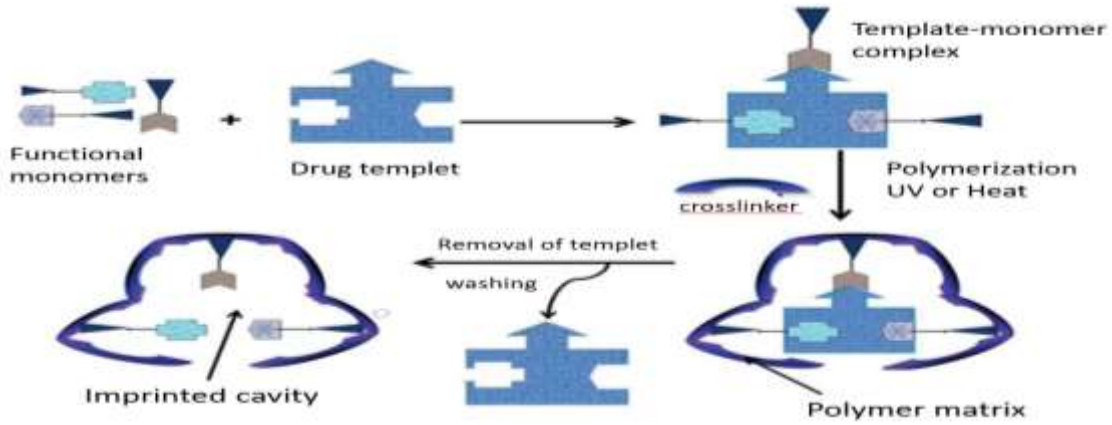

Figure 2 : Schematic representation of MI process using drug as a template(34)

Table 3: Summary of Treatment Methods and Findings for Ophthalmic Fungal Keratitis

disorders of the eyes	Technique	Active principle	Conclusions/Outcomes
Fungal keratitis	NPs	Silver NPs, voriconazole	In seven days, alleviate fungal keratitis
	Nanocoatings	Gallic acid, tobramycin	demonstrated notable antimycotic, biofilm-inhibiting, and antifouling qualities.
	Vitamin E	Levofloxacin, chlorhexidine	Levofloxacin and chlorhexidine with extended release times of up to 100 hours and 170 hours, respectively
	DPF	Econazole	Keep the fungicidal rate at 100% for three weeks.

Conclusion

Therapeutic contact lenses (TCLs) represent a significant advancement in ocular drug delivery, offering improved bioavailability and patient compliance compared to traditional eye drops. By providing extended and controlled release of antifungal drugs, TCLs address the challenges associated with treating fungal keratitis, such as frequent dosing and poor drug penetration. Various innovative methods for drug incorporation, including molecular imprinting and polymer nanoparticles, have shown promising results in enhancing drug loading and release profiles. Overall, TCLs have the potential to revolutionize the treatment of ocular infections, improving patient outcomes and quality of life.

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