



Contents lists available at ScienceDirect

Survey of Ophthalmology

journal homepage: www.elsevier.com/locate/survophthal

Review article

Pharmacologic principles behind eye drop dosing: From pharmacokinetics to clinical practice

Luca Lucchino, MD^{a,b}, Enrico Giuliano^c, Ferdinando Giuliano^d, Riccardo Chiorrini, MD^a,
 Francesco Semeraro, MD^{a,e}, Lorenzo Drago, BSc PhD^{f,g}, Mariantonia Ferrara, MD^{a,e,*},
 Vito Romano, MD^{a,e}

^a Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy^b Department of Sense Organs, Sapienza – University of Rome, Rome, Italy^c Faculty of Medicine and Surgery, University of Sassari Medical School, Sassari, Italy^d Department of Biomedical Sciences, Humanitas University, Rozzano, Milan, Italy^e Eye Unit, ASST Spedali Civili di Brescia, Brescia, Italy^f UOC Laboratory of Clinical Medicine with Specialized Areas, IRCCS MultiMedica, Milan, Italy^g Clinical Microbiology and Microbiome Laboratory, Department of Biomedical Sciences for Health, University of Milan, Milan, Italy

ARTICLE INFO

Keywords:

Topical ocular pharmacology
 Pharmacokinetics
 Pharmacodynamics
 Dosing regimen
 Anti-inflammatory drugs
 Corticosteroids
 Immunomodulators
 Antimicrobial therapy
 Nanocarriers
 Ocular drug delivery

ABSTRACT

Topical ocular therapy plays a crucial role in managing infectious and inflammatory diseases of the anterior segment. Its therapeutic efficacy depends not only on the intrinsic potency of the drug, but also on the appropriateness of the dosing regimen in relation to ocular pharmacokinetics and pharmacodynamics principles. Because less than 5% of an instilled dose reaches the intraocular tissues, achieving therapeutic efficacy requires tailoring dosing schedules to tear dynamics, barrier permeability, and formulation characteristics. Despite its central relevance to clinical outcomes, the application of pharmacokinetics/pharmacodynamics (PK/PD) principles to topical ocular therapy remains under-recognized and often inconsistently applied in routine practice. In this light, this review integrates experimental and clinical evidence on how pharmacologic principles guide the dosing of anti-microbial and anti-inflammatory agents. Among antibiotics, aminoglycosides benefit from high early peaks (peak concentration/minimum inhibitory concentration [MIC]-driven), fluoroquinolones from sustained exposure (area under the curve/MIC-driven), and β -lactams from continuous time above MIC ($T > MIC$). These PK/PD parameters must also take into account the pathogen's susceptibility in addition to the intrinsic bacteriostatic or bactericidal activity of the drug. Similarly, corticosteroid and immunomodulator regimens require controlled loading and tapering to balance efficacy and safety, particularly in graft care and ocular surface disease. Advances in preservative-free systems, nanocarriers, and stimuli-responsive formulations promise greater precision, lower toxicity, and improved adherence. Integrating PK/PD-guided strategies into daily practice offers a rational framework for optimizing topical ocular pharmacotherapy across drug classes.

1. Introduction

Topical ocular drug delivery remains the cornerstone for treating anterior segment diseases, owing to its simplicity, safety, and direct drug access to target tissues; however, its pharmacokinetics profile differs significantly from systemic routes due to the eye's unique anatomy and physiology. Rapid tear turnover, limited corneal permeability, and multiple anatomical barriers sharply restrict intraocular bioavailability, with additional losses related to blinking and nasolacrimal drainage that

further limit pre-corneal residence time of topically administered formulations.^{1,2} As a result, the efficacy of ocular pharmacotherapy depends not only on the intrinsic potency of the drug but also on the factors influencing pharmacokinetics and pharmacodynamics (PK/PD), including physicochemical properties of its formulation, the dynamics of tear film and ocular surface, and the clinical condition of the recipient eye, together with formulation-related parameters such as particle size, surface characteristics, and the balance between muco-adhesion and muco-penetration that influence ocular drug exposure.¹ Growing

* Corresponding author at: Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy.

E-mail address: mariantonia.ferrara@unibs.it (M. Ferrara).

<https://doi.org/10.1016/j.survophthal.2026.03.012>

Received 30 November 2025; Received in revised form 11 March 2026; Accepted 16 March 2026

Available online 18 March 2026

0039-6257/© 2026 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

attention has therefore been directed toward the PK/PD principles that underlie ocular dosing. We synthesize current knowledge of ocular PK/PD, focusing on the role of formulation parameters, ocular physiology, and clinical context on drug exposure and response. We also explore the influence of recipient ocular conditions on drug kinetics and efficacy. We highlight emerging directions in PK/PD-guided posology, nanomedicine and precision dosing as potential avenues to overcome longstanding barriers in topical ocular drug delivery.^{3–5}

2. Ocular pharmacokinetics and pharmacodynamics basics

The eye is highly compartmentalized and protected because of a set of partially isolated micro-compartments separated by tight anatomical and physiological barriers. Consequently, ocular PK/PD differs fundamentally from systemic PK/PD because, unlike systemic administration, ocular delivery must overcome rapid precorneal clearance, limited contact time, and multiple anatomical barriers, all of which drastically reduce intraocular bioavailability and complicate therapeutic dosing.^{6–8} More specifically, after topical dosing, drug disposition is governed by precorneal loss (tear turnover and drainage), partitioning into the cornea and conjunctiva, and subsequent distribution into the aqueous humor and potentially deeper tissues. After intraocular delivery, additional barriers and slow clearance mechanisms determine exposure in the vitreous and retina. These barriers create pronounced concentration gradients across ocular tissues, meaning that plasma PK is generally not a reliable surrogate for ocular exposure, especially for posterior-segment targets. Consequently, ocular pharmacodynamics should be interpreted in the context of the relevant ocular compartment (i.e., tear film/corneal epithelium for surface disease; aqueous humor for anterior-segment targets; vitreous/retina for posterior-segment targets), as the PK driver of effect (peak concentration [C_{max}], area under the curve [AUC], residence time) and the PD endpoints (e.g., epithelial integrity, inflammation markers, intraocular pressure, retinal outcomes) are typically compartment-specific rather than systemically determined. This compartmentalization is a major reason why optimized ophthalmic formulations prioritize local residence time and tissue-specific permeability while simultaneously limiting off-target⁹.

2.1. Pharmacokinetics and pharmacodynamics interplay in ocular therapy

PK is the quantitative study of drug absorption, distribution, metabolism, and elimination and the resulting concentration–time profile in the body.¹⁰ Applied to ophthalmology, PK focuses on drug concentrations in the target ocular compartments, most commonly the corneal stroma and the aqueous humor. Key PK descriptors include C_{max} (peak concentration), AUC over the dosing interval, often 24 h, T_{max} (time to peak), and T_{1/2} (terminal half-life). PD is the quantitative study of the relationship between drug concentration at the site of action and the magnitude and time course of the biological effect, governed by mechanism of action and receptor interactions/occupancy.¹¹ In ocular therapy, PK and PD are tightly coupled because precorneal loss and epithelial barriers determine whether drug concentrations in the corneal stroma or aqueous humor reach the levels required to achieve the intended effect.⁴ For anti-infective agents, the ability of the drug to achieve therapeutically effective concentrations at the site of infection is often limited by ocular barriers and clearance.¹² Thus, *in vitro* sensitivity, typically expressed as the minimum inhibitory concentration (MIC), must be interpreted in the context of local ocular drug levels. In human ocular penetration studies, topical fluoroquinolones achieve measurable corneal stromal concentrations, commonly reported on the order of 10–20 µg/g, albeit with marked interindividual variability.^{13,14} Aqueous humor concentrations are substantially lower, typically within the 0.1–0.5 µg/mL range after short preoperative dosing regimens.^{13,15} With more intensive instillation schedules, higher aqueous levels have been reported for specific agents; specifically, topical moxifloxacin

achieved mean aqueous concentrations of 0.88 µg/mL with q6h dosing and 2.28 µg/mL with q2h dosing.¹⁶ In contrast to fluoroquinolones, vancomycin displays a pronounced compartmental distribution following topical administration. Fortified topical vancomycin (33 mg/mL) reaches very high corneal stromal concentrations, with a reported mean of approximately 46.7 µg/g¹⁷, while aqueous humor concentrations remain markedly lower; after topical administration of vancomycin 50 mg/mL, mean aqueous levels of approximately 0.22 µg/mL have been reported.¹⁸

These measured tissue concentrations should be interpreted alongside *in vitro* susceptibility data, particularly MIC₉₀ values, defined as the minimum inhibitory concentration required to inhibit the growth of 90% of tested isolates.¹⁹ In bacterial keratitis isolates, fluoroquinolone MIC₉₀ values for *Pseudomonas aeruginosa* typically range from 0.25 to 4 µg/mL, depending on the specific agent.^{20,21} In contrast, MIC₉₀ values for *Staphylococcus aureus* are lower for methicillin-susceptible strains (e.g., moxifloxacin MIC₉₀ approximately 0.5 µg/mL), but substantially higher for methicillin-resistant isolates (MRSA), with reported moxifloxacin MIC₉₀ values of up to 32 µg/mL²¹. By comparison, vancomycin MIC₉₀ values for *Staphylococcus aureus*, including MRSA, consistently remain low (approximately 1 µg/mL).^{21,22} Accordingly, MIC values for ocular pathogens should be interpreted in relation to the concentrations that topical therapy is able to achieve within ocular tissues.

If the drug does not reach concentrations above the MIC at the site of infection, clinical failure can occur despite apparent susceptibility.¹⁹ These discrepancies may depend not only on the PK/PD factors discussed above, but also on the frequent presence of biofilm in ocular infections, which can render the causative microorganism functionally tolerant or insensitive to antibiotics even when planktonic MIC values are low.²³ In addition, the bacteriostatic or bactericidal profile of an antibiotic is not an intrinsic binary property, but depends on its concentration relative to the MIC and the minimum bactericidal concentration (MBC), the lowest concentration required to achieve ≥ 99.9% bacterial kill. Agents with an MBC/MIC ratio ≤ 4 are generally considered bactericidal, while higher ratios suggest a bacteriostatic effect.²⁴ Moreover, the minimum toxic concentration (MTC) defines the upper bound of the therapeutic window: beyond this threshold, toxicity is expected to occur.²⁵

2.1.1. PK/PD indices

Integrating drug exposure with microbiological potency yields three PK/PD indices used to predict antimicrobial efficacy: 1) T > MIC (the fraction of the dosing interval during which drug concentration in the target compartment remains above the minimum inhibitory concentration), 2) C_{max}/MIC (the ratio of peak concentration to MIC), and 3) AUC/MIC (the 24-hour area under the concentration–time curve divided by MIC).²⁶ Each index captures a distinct dimension of pharmacologic exposure, and different antimicrobial classes correlate with different drivers of efficacy: β-lactams are time-dependent (linked to T > MIC), aminoglycosides are concentration-dependent (linked to C_{max}/MIC), and fluoroquinolones are exposure-dependent (correlating best with AUC/MIC, with a secondary role for C_{max}/MIC).²⁷ Because ocular bioavailability after topical administration is limited, posologic strategies, particularly loading, maintenance, and tapering, should be optimized according to the PK/PD index most predictive of efficacy for the antimicrobial class (Fig. 1).²⁸

To enhance clinical usability, we here report how quantitative PK/PD targets commonly used for fluoroquinolones in the different infections can be extrapolated and operationalized for ocular infections. Fluoroquinolones exhibit concentration-dependent killing, and both AUC/MIC and C_{max}/MIC have been linked to clinical and microbiological success as well as resistance suppression. A frequently cited target range for many Gram-negative pathogens is AUC/MIC ~100–125 (and/or C_{max}/MIC >10), while data in *S. pneumoniae* suggest that an AUC/MIC < 40 may better predict efficacy.²⁹ Although these thresholds were largely derived from systemic/respiratory infection datasets, it

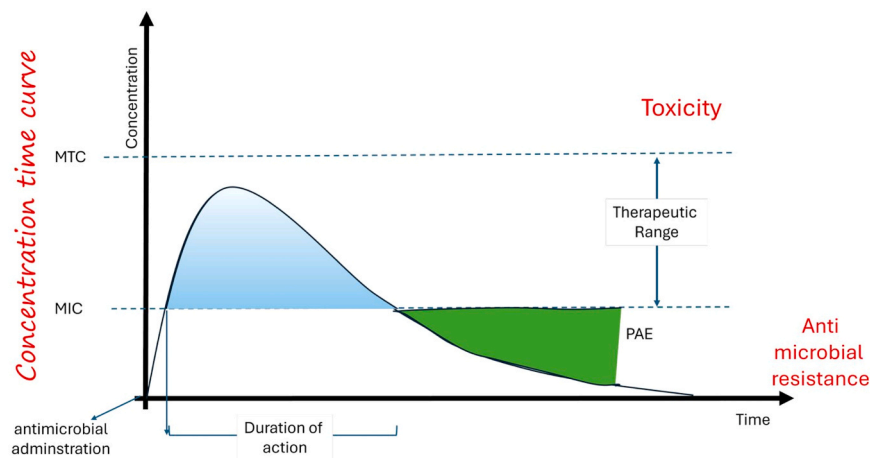


Fig. 1. Pharmacokinetic concentration–time curve illustrating the therapeutic window. The graph shows a typical drug concentration–time curve following a single dose. The Minimum Inhibitory Concentration (MIC) marks the lower limit of the therapeutic range, below which antimicrobial efficacy is lost and resistance selection may occur (green zone). The Minimum Toxic Concentration (MTC) defines the upper boundary, above which toxicity may emerge. The blue-shaded area represents the duration during which the drug concentration remains within the therapeutic window, high enough to inhibit bacterial growth without causing toxicity. PAE: Post Antibiotic effect.

could be predictable to use them as reference targets to be interpreted in ocular exposure metrics when direct ocular outcome-linked thresholds are unavailable. In an ocular context, of course, these targets should be applied by estimating local ocular exposure (e.g., tear film and/or corneal tissue AUC and peak concentrations after topical dosing) and comparing these exposures to MIC values from corneal isolates. Where only systemic-derived targets exist, they are presented as pragmatic reference thresholds, and we explicitly would emphasize the need for future studies linking ocular compartment exposure to corneal infection outcomes.^{30,31}

2.2. Barriers - tear film, cornea, conjunctiva, nasolacrimal drainage

The 7–10 μL tear film (turnover $\sim 1 \mu\text{L}/\text{min}$) rapidly dilutes instilled drops; typical commercial volumes ($> 30 \mu\text{L}$) overflow into the nasolacrimal pathway, promoting systemic absorption and leaving $< 5\%$ to reach intraocular tissues.¹⁰ The cornea lipophilic tight-junction epithelium, hydrophilic stroma, and weakly lipophilic endothelium acts as a

biphasic barrier, so efficient passage generally requires amphipathic properties. The conjunctiva is more permissive to hydrophilic/macromolecular drugs, but its vascular and lymphatic beds favor systemic uptake, reducing local bioavailability. Although emphasized for systemic therapy, the blood-aqueous barrier (BAB) nonfenestrated iris vasculature and tight junctions in the non-pigmented ciliary epithelium can still influence topically applied agents by facilitating efflux of lipophilic compounds from the anterior chamber to blood, thus altering residence time and efficacy.^{6,7} Fig. 2 provides a schematic summary of the pathways and barriers involved in topical drug absorption.

2.3. Routes of absorption and elimination

Entry is predominantly transcorneal for small, moderately lipophilic molecules (optimal for the anterior chamber [AC]) or conjunctival/scleral for hydrophilic/macromolecular agents (typically lower intraocular levels). After entry, clearance proceeds via trabecular and

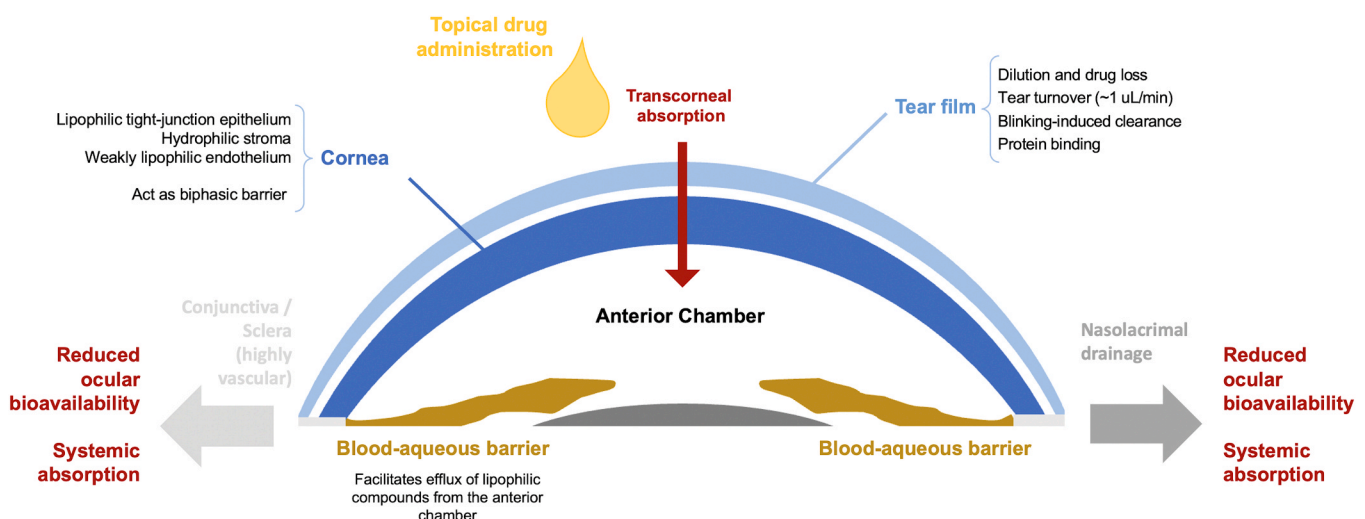


Fig. 2. Schematic overview of pathways and barriers involved in topical ocular drug absorption. Following topical administration, drugs primarily enter the eye via transcorneal absorption into the anterior chamber. The cornea presents multiple barriers, including the lipophilic epithelium, hydrophilic stroma, and endothelium, which together restrict drug permeation. Additional loss mechanisms include tear film dilution and turnover, blinking-induced clearance, and nasolacrimal drainage, all of which reduce ocular bioavailability and may contribute to systemic absorption. Drug distribution within the anterior chamber is further limited by the blood-aqueous barrier, which regulates exchange between ocular tissues and the systemic circulation.

uveoscleral outflow; lipophilic drugs are removed more rapidly with uveal blood flow. Ocular metabolism features low cytochrome P450 expression but abundant esterases, which contribute to local clearance and activate ester pro-drugs, thereby shaping intraocular bioavailability.^{6,8}

2.4. Local vs systemic bioavailability

Topical dosing yields highly variable, generally low intraocular drug concentration. Models relate AC penetration to molecular radius, lipophilicity (octanol–water partition, Φ), volume of distribution (V_d), and clearance (Cl_a). In humans, predicted bioavailability is ~1–5% for lipophilic drugs ($\Phi > 1$) and < 0.5% for hydrophilic agents ($\Phi < 0.01$).³² Exposure may improve by lowering the conjunctival-to-corneal permeability ratio and limiting nasolacrimal loss. Despite the local intent, systemic absorption via conjunctiva and especially nasal mucosa, both highly vascularized, bypass first-pass metabolism and can be clinically relevant⁷; for example, timolol can achieve plasma levels sufficient for β -blockade and bradycardia at standard doses.³³

2.5. Tear turnover, blinking, and retention time

Tear turnover and blinking significantly decrease the ocular surface residence time of topically applied drugs. Fluorophotometric studies demonstrate a characteristic biphasic decay in tear fluorescein concentration after instillation, with a rapid early phase driven by reflex tearing and blinking, followed by a slower basal phase reflecting steady-state tear turnover estimated at ~0.5–2 $\mu\text{L}/\text{min}$.³⁴ Consistent with this, substantial precorneal drug clearance occurs within approximately 2–5 min after dosing.^{7,35} Under ocular surface irritation or inflammatory stimulation, protective reflexes further accelerate precorneal clearance. Experimental ocular surface stimulation markedly reduces interblink interval (from ~9.5 s to ~1.4 s) and increases blink rate (up to ~110 blinks/min), enhancing nasolacrimal drainage³⁶. In parallel, reflex lacrimation increases tear flow to ~50 $\mu\text{L}/\text{min}$, with maximal estimates approaching ~100 $\mu\text{L}/\text{min}$, thereby prolonging the rapid-clearance regime and further shortening ocular surface residence time.^{37,38}

Increasing viscosity or incorporating mucoadhesive polymers (e.g., hyaluronic acid/biopolymers) prolongs retention in humans, sometimes several-fold versus saline³⁹, which can be leveraged to enhance absorption and reduce dosing frequency.

3. The physics and formulation of eye drops

Topical ocular therapy relies not only on the pharmacologic properties of the active compound, but also on the physicochemical and technological characteristics of the eye drop formulation. These factors influence precorneal residence time, corneal permeability, patient tolerability, and ultimately therapeutic efficacy.

3.1. Drop volume, pH, osmolality, and lipophilicity

Conventional dispensers deliver 30–50 μL per actuation, well above the tear reservoir of ~7 μL . The excess promotes overflow and reflex tearing, accelerating nasolacrimal loss; in practice, a single instillation suffices and sequential drops should be avoided.^{7,40} Tolerability is optimized when the formulation approaches the tear pH (~7.4) and remains within a workable window (~6.6–7.8); buffering allows maintenance of comfort when solubility or stability impose suboptimal pH.^{41,42} Likewise, osmolality near 290–310 mOsm/L supports tear film stability and epithelial integrity.^{43–45} Corneal transport is favored by amphipathic molecules with intermediate lipophilicity, whereas highly hydrophilic agents more readily exploit conjunctival–scleral pathways; aligning the formulation with the intended route improves exposure at the target tissues.⁴⁰

3.2. Solutions, suspensions, emulsions, and gels

Aqueous solutions remain the workhorse for daytime therapy because they provide immediate drug availability and predictable initial ocular pharmacokinetics; however, solutions are characterized by rapid clearance, leading to short residence time and limited ocular bioavailability. The use of viscosity enhancers or mucoadhesive polymers (e.g., hyaluronic acid, carbomers, methylcellulose) can modestly prolong residence time and increase drug exposure, although excessive viscosity may reduce patient comfort and reflex tearing, counteracting PK benefits.^{7,44,46}

Suspensions enable delivery of poorly water-soluble drugs and may provide prolonged ocular exposure through gradual dissolution of drug particles in the tear film. In terms of PK profile, this can result in a depot effect at the ocular surface, extending absorption time; however, suspensions exhibit greater inter-dose variability, require shaking to ensure dose uniformity, and may elicit foreign-body sensation.⁴⁷

Oil-in-water emulsions improve solubilization and corneal epithelial penetration of lipophilic agents, enhancing partitioning into ocular tissues and potentially increasing intraocular bioavailability, as clinically exemplified by cyclosporine.^{40,48} Nonetheless, emulsions may be associated with transient visual blur, ocular discomfort, and formulation instability, which can negatively impact adherence and effective dosing.

Gels and ointments provide the longest precorneal residence time and enable sustained drug release resulting in prolonged ocular exposure and reduced dosing frequency. These PK advantages are offset by significant visual blurring, and reduced daytime tolerability, confining their use primarily to nighttime administration or severe ocular surface disease.⁴⁹

Finally, when enhanced retention or solubilization is required without increasing dosing frequency, in-situ gelling systems, cyclodextrin-based carriers, and nanostructured delivery platforms are reasonable options offering intermediate PK profiles by combining acceptable tolerability with improved residence time and tissue exposure.^{44,50,51}

3.3. Impact of preservatives on absorption and toxicity

Quaternary ammonium preservatives, notably benzalkonium chloride (BAK), are effective antimicrobials but perturb the ocular surface. More specifically, preservatives can affect ocular absorption through two mechanistically distinct and temporally different processes, namely short-term permeability enhancement (“junction-opening”/barrier perturbation) and long-term ocular surface toxicity (epithelium and goblet-cell/secretory apparatus).

In the short term, surfactant preservatives such as BAK have been shown to disrupt epithelial tight junctions, alter epithelial cell membrane integrity and induce superficial epithelial desquamation¹¹. These structural changes perturb the corneal epithelial barrier and can transiently increase paracellular permeability and transiently enhance drug penetration of topically applied drugs, particularly hydrophilic or poorly permeable compounds;⁵² however, this effect is dose- and time-dependent and primarily observed when the corneal epithelium is already compromised or with repeated exposure⁵³. In clinical-relevant settings, preservative-containing formulations have been associated with worsened epithelial barrier function compared with preservative-free tears, consistent with preservative-driven barrier disruption.

On the other hand, repeated exposure to preservatives, particularly in chronic therapies, is consistently associated with cumulative ocular surface toxicity, characterized by epithelial stress, reduced goblet cell density, destabilization of the tear film, apoptosis in corneal and conjunctival cells and inflammatory/oxidative pathways, ultimately compromising surface homeostasis and tolerance.^{11,54} *In vitro*, BAK-preserved ophthalmic combinations produce significantly greater conjunctival epithelial cell toxicity, including reduced viability and

increased apoptosis/oxidative stress, compared with less cytotoxic preservative systems (e.g., polyquaternium-1) or preservative-free approaches.⁵⁵ Confocal microscopy studies have also demonstrated sub-basal nerve fiber damage following chronic BAK exposure, contributing to ocular discomfort and neurogenic inflammation.⁵⁶

Clinically, this distinction matters because a formulation that transiently increases permeability does not necessarily improve therapeutic performance if chronic dosing progressively damages the ocular surface and worsens symptoms, adherence, and long-term safety. For long-term therapy or preexisting ocular surface disease, preservative-free presentations, via unit-dose packaging or advanced multidose valves, are therefore preferred.

3.4. Advanced delivery systems: nanocarriers and beyond

Innovative ocular delivery platforms are designed to mitigate low corneal permeability, rapid precorneal clearance, and poor solubility. Among them, key emerging platforms include nanocarriers, polymeric nanoparticles, nanomicelles, and dendrimers, as well as chitosan-coated systems and stimuli-responsive hydrogels. Table 1 summarizes the structural characteristics, delivery mechanisms, and reported advantages of key nanocarriers and advanced delivery carriers currently investigated to enhance corneal penetration, prolong precorneal residence time, improve bioavailability, and enable targeted ocular therapy.

Nanocarriers, including liposomes, polymeric nanoparticles (e.g., PLGA), nanomicelles, and dendrimers, can increase bioavailability by improving solubilization, prolonging residence, and enabling controlled release and targeting.^{44,50,51,57,58} Liposomes encapsulate both hydrophilic and lipophilic drugs and can facilitate epithelial passage. Polymeric nanoparticles provide sustained release and extended tissue exposure.^{51,59} Nanomicelles from amphiphilic copolymers are effective for poorly soluble agents (e.g., voriconazole, dexamethasone) and, owing to sub-100 nm size, may reduce precorneal clearance and support penetration, particularly when ocular surface permeability is increased by inflammation.⁴⁴ Dendrimers offer high payload capacity and surface

functionalization for targeted delivery, with early studies suggesting favorable tolerability.^{60,61} Surface chitosan-coating can enhance mucoadhesion and residence on the ocular surface.⁵¹ Looking ahead, stimuli-responsive (temperature/pH) hydrogels and ligand-targeted carriers aim to lower dosing frequency, limit off-target exposure, and increase tissue selectivity.^{50,62–66}

These approaches are particularly attractive in anterior segment disease, such as dry eye and ocular inflammation, where longer retention and controlled release can translate into practical clinical benefit.

4. The clinical impact of recipient ocular conditions on dosing strategy

The condition of the recipient can also impact on ocular drug exposure. Indeed, inflammation, surgical changes, and ocular surface disease alter barrier permeability and tear-film clearance, requiring tailored dosing to maintain efficacy and safety.

4.1. Inflamed or infected eye: barrier disruption and dosing strategy

Ocular inflammation, infectious or sterile, remodels ocular pharmacokinetics by disrupting the BAB and the corneal epithelium, which normally limit drug penetration. Inflammatory cytokines increase iris vascular permeability and loosen tight junctions within the ciliary epithelium, permitting greater influx of plasma proteins and circulating drugs into the aqueous humor. This creates a pharmacokinetic “paradox”: systemic agents may achieve higher intraocular exposure than topical drops because of several factors determining underexposure, including early reflex tearing, increased blinking, mucin disruption, and faster tear turnover accelerate washout.^{7,67} On the contrary, in a healthy eye the efficacy of systemic routes is limited by the blood ocular barrier that restricts intraocular drug levels.⁶⁸

In addition, in inflamed eyes, particularly in microbial keratitis and severe anterior uveitis, standard topical dosing is often insufficient; to counter increased permeability and accelerated clearance, clinicians use loading regimens with high frequency instillation (every 15–60 min) to rapidly achieve therapeutic levels across disrupted barriers.^{7,69} Inflammation increases aqueous protein leakage that binds lipophilic drugs, lowering the free active fraction.⁷⁰ Corneal neovascularization provides leaky routes that may increase penetration even for larger molecules, although quantitative human PK data remain limited.

Biofilm formation further complicates topical antibiotic therapy. These structured bacterial communities, embedded in an extracellular matrix, are far more tolerant than free-floating (planktonic) organisms, reported up to ~1000 fold higher drug concentrations required, and better evade host defenses.⁷¹ Several clinically relevant microorganisms exhibit a well-recognized propensity to form biofilms in ocular infections, most notably *Pseudomonas aeruginosa*, *Staphylococcus aureus* (including MRSA), and coagulase-negative staphylococci. Additional contributions from Gram-negative bacteria such as *Escherichia coli* and fungal species including *Candida albicans* have also been documented.^{72–74} They commonly develop on ocular tissues and on devices such as contact lenses and sutures, sustaining chronic or relapsing infection. Biofilm-associated infections exhibit reduced antibiotic susceptibility through multiple concurrent mechanisms. The extracellular matrix can act as a diffusion barrier and, in some settings, sequester antimicrobial molecules (e.g., via binding to extracellular DNA), thereby delaying or reducing effective drug penetration to embedded cells^{75,76}. In parallel, steep gradients of oxygen, nutrients, and pH within the biofilm microenvironment reduce antimicrobial activity and generate marked physiological heterogeneity.⁵³ High bacterial density within biofilms can further diminish antibiotic efficacy for selected drug classes, consistent with an inoculum effect.⁷⁵ Moreover, a substantial fraction of biofilm-associated bacteria adopt slow-growing or metabolically quiescent states, including persister cells, which reduces the effectiveness of agents that require active growth or metabolism⁷⁶. In addition,

Table 1

Structural characteristics, delivery mechanisms, and reported advantages of key nanocarriers and advanced delivery carriers.

Carrier	Mechanism	Advantages
Liposomes	Phospholipid bilayer vesicles encapsulating hydrophilic and lipophilic drugs; facilitate penetration through the corneal epithelium	Enhanced bioavailability/penetration
Polymeric nanoparticles (e.g., PLGA)	Biodegradable particles enabling controlled release; prolonged retention in ocular tissues	Controlled release; prolonged tissue retention
Nanomicelles	Assemblies of amphiphilic copolymers; size < 100 nm	Effective for poorly soluble drugs; small size may reduce tear clearance and promote penetration, especially in inflamed tissues
Dendrimers	Branched macromolecules with functional surface groups; high drug-loading; modifiable for targeted delivery	Improved bioavailability and tolerability reported in early trials
Chitosan-coated nanoparticles	Chitosan coating to increase mucoadhesion and residence time on the ocular surface	Increased precorneal residence; enhanced absorption in preclinical models
Stimuli-responsive hydrogels	Temperature or pH sensitive hydrogels	Aim to reduce dosing frequency, minimize side effects, and improve targeted delivery
Ligand-targeted nanocarriers	Nanocarriers functionalized with ligands to deliver drugs to specific cell types	Targeted delivery; potential reduction of off-target effects and dosing frequency

biofilm-associated cell–cell signaling (quorum sensing) coordinates stress responses, matrix production, and tolerance phenotypes, further stabilizing the biofilm and limiting antimicrobial effectiveness.⁷⁵ The close spatial organization within biofilms also facilitates horizontal gene transfer, promoting antibiotic resistance and the persistence of chronic or relapsing infections.⁷⁷ When biofilm is suspected, management typically includes loading with high frequency topical antibiotics, consideration of fortified concentrations and dual coverage, plus night time ointment and debridement or device removal, followed by reassessment at 24–48 h. If the response is inadequate, escalate the route. removal, followed by reassessment at 24–48 h. If the response is inadequate, escalate the route.⁷⁸ Experimental anti-biofilm strategies remain largely investigational. Preclinical studies have investigated agents specifically designed to destabilize biofilm structure, including compounds that enzymatically degrade extracellular matrix components and quorum-sensing inhibitors that disrupt biofilm-associated signaling pathways, ultimately reducing biofilm stability and tolerance phenotypes.^{75,79} Furthermore, advanced drug delivery systems have been developed to improve antimicrobial activity against biofilm-associated pathogens.⁸⁰ Among these, nanotechnology-enabled platforms can enhance local drug retention, improve penetration into biofilms, and provide sustained antimicrobial exposure at the site of infection. Pre-clinical evidence suggests that these systems may interact with biofilm matrix components or exploit biofilm-specific microenvironmental features, such as acidic pH, localized enzymatic activity, or increased levels of reactive oxygen species, to enhance targeting and antimicrobial efficacy *in vitro* and in selected *in vivo* models.⁸¹ Despite these promising findings, these strategies have not yet been validated and therefore do not currently modify standard therapeutic recommendations.^{77,81}

4.2. Post-operative and transplanted cornea: fragility, immunity, and tailored dosing

Ocular surgery, particularly corneal transplantation (penetrating or lamellar keratoplasty), induces profound structural and immunologic changes that affect drug pharmacokinetics and dosing strategies. In the immediate postoperative period, the cornea presents with disrupted epithelial integrity, altered stromal hydration, and compromised barrier function. These factors can transiently enhance permeability to topically applied drugs, but also increase vulnerability to toxicity, especially from preservatives or high-dose regimens; however, the pharmacokinetic profile of transplanted eyes is deeply influenced by a more complex, evolving variable: the breakdown of ocular immune privilege. The cornea is typically protected from systemic immune activation by the absence of vasculature, low MHC expression, and active immune regulatory mechanisms (such as anterior chamber-associated immune deviation, or ACAID).⁸² Surgical trauma, neovascularization, and inflammation can dismantle these mechanisms, exposing the graft to host immune surveillance. This immunologic shift has both clinical and pharmacologic consequences. Inflammatory neovascularization introduces new, aberrant vascular pathways that not only permit immune cell infiltration but may also facilitate altered drug access into the corneal stroma. Moreover, the inflamed environment can alter drug clearance kinetics via increased enzymatic activity and barrier leakage, although specific pharmacokinetic studies in this context remain scarce.^{6,83}

High-risk corneal grafts, those with preexisting inflammation, prior rejection, or deep vascularization, require long-term, intensive immunosuppression. Standard corticosteroids remain the first-line agents, but prolonged use increases the risk of infection, delayed healing, and glaucoma. In these settings, adjunctive immunomodulators such as topical cyclosporine A or tacrolimus are frequently employed. These agents have been shown not only to reduce rejection risk but also to maintain epithelial integrity better than corticosteroids alone in certain contexts.²⁶

Corneal neovascularization with lymphangiogenesis enables APC

migration to nodes, priming naïve T cells and accelerating rejection.⁸⁴ Topical vascular endothelial growth factor-C/D blockade suppresses lymphangiogenesis but doesn't prolong graft survival in mice, likely due to compensatory immune pathways.⁸⁵ Importantly, post-keratoplasty eyes are particularly susceptible to infectious complications, which can significantly compromise graft survival. Multiple factors contribute to this heightened vulnerability, including persistent epithelial defects, exposed or loose sutures, prolonged use of corticosteroids, and altered ocular surface flora.⁸² These elements create a permissive microenvironment for microbial colonization, especially by opportunistic pathogens. Fungal organisms such as *Candida* and *Fusarium* are increasingly recognized as leading causes of infectious keratitis and graft failure, particularly in tropical regions and among patients on long-term topical corticosteroids.⁸⁶ The avascular nature of the graft and local immunosuppression further impair immune surveillance and drug delivery, complicating eradication efforts. In such settings, clinicians must promptly adjust the therapeutic regimen. This often involves temporary withdrawal of corticosteroids and the initiation of targeted antimicrobial therapy.⁸⁷ Topical calcineurin inhibitors, such as cyclosporine A or tacrolimus, may be introduced as steroid-sparing agents, providing immunomodulation while minimizing pathogen proliferation.⁸⁴ Recognizing early signs of infection and tailoring both antimicrobial and immunosuppressive strategies are essential to preserving graft function in this delicate pharmacological context.

4.3. Dry eye and ocular surface disease: tear-film instability, epithelial barrier dysfunction, and formulation-driven dosing

Dry eye disease (DED) is defined as a multifactorial, symptomatic condition characterized by loss of tear film and/or ocular surface homeostasis, involving tear instability, hyperosmolarity, inflammation, and neurosensory dysfunction.⁸⁸ This framework explains the frequent sign-symptom discordance and highlights that pharmacologic decisions must be tailored to the individual's etiological drivers (lipid, aqueous, mucin/glycocalyx deficiency; eyelid/blink anomalies; ocular surface abnormalities). Shortened tear film break-up time (TBUT), reduced tear volume, mucin/glycocalyx disruption, and increased osmolarity impair uniform spreading of standard drops, shorten residence time, and increase concentration spikes that can exacerbate burning and reflex tearing.⁸⁸ From a pharmacokinetic standpoint, these alterations result in heterogeneous precorneal drug distribution, increased intra- and inter-individual variability in surface exposure, and reduced predictability of the delivered dose. Because precorneal residence in DED is intrinsically short and highly variable, effective drug exposure depends on formulations that stabilize the tear film–epithelial interface and ensure uniform precorneal distribution. HP guar/borate gels stabilize the tear film, lower osmolarity, aid epithelial repair, and prolong residence, while hyaluronic acid improves symptoms and staining. Lipid emulsions and perfluorohexyloctane reduce evaporation and improve TBUT and comfort, with trials supporting perfluorohexyloctane four times daily and benefits by 15 days with usually mild transient blur.⁸⁹

Given the fragility of the injured surface, preservatives (eg BAK) exacerbate epithelial, neural, and goblet-cell toxicity and raise osmolarity. Consequently, preservative-free unit-dose or PF-multidose systems are preferred for chronic use, with systematic reviews and real-world studies noting better TBUT, Schirmer, and symptom outcomes after switching from preserved drops.^{88,90} Similarly, osmoprotective compositions (e.g., trehalose or polyols) and hypoosmotic designs help buffer hyperosmolar stress and support epithelial homeostasis. This approach aligns with the DEWS framework that targets the vicious circle in which tear film instability leads to hyperosmolarity, which triggers inflammation and ultimately causes surface damage (DEWS Digest). Inflammatory signaling, characterized by upregulation of cytokines (IL-1 β , IL-6, IL-8, TNF- α) and proteolytic enzymes such as MMP-9, drives immune-mediated remodeling of the corneal epithelial barrier through damage to the glycocalyx and intercellular tight junctions. The epithelial

glycocalyx is a hydrated steric and electrostatic barrier that limits direct solute access while regulating surface wettability. In DED, inflammatory degradation of this layer exposes the apical epithelium to hyperosmolar and inflammatory stress, reducing constraints on drug access and increasing variability in epithelial exposure, particularly for hydrophilic and charged compounds.^{91,92} Concomitantly, inflammatory remodeling of the ocular surface disrupts epithelial tight junctions through MMP-9-mediated cleavage and redistribution of occludin and ZO-1, leading to loss of paracellular sealing and increased permeability to hydrophilic solutes.⁹³ Hyperosmolar stress amplifies this MMP-driven junctional breakdown, further compromising the epithelial diffusion barrier.⁵² Barrier damage results in a quantifiable increase in corneal epithelial permeability, with fluorophotometric studies demonstrating up to 3- to 3-fold increases in stromal uptake of sodium fluorescein in DED patients compared with healthy controls.⁹⁴ Moreover, fluorescein penetration correlates with corneal epithelial staining severity, indicating that progressive barrier disruption is associated with increasing solute permeability.³⁵ From a pharmacokinetic perspective, this barrier breakdown implies increased and more variable trans-epithelial drug flux, particularly for hydrophilic and paracellularly transported compounds, with reduced predictability of effective tissue exposure.

Controlling this inflammatory milieu is therefore central to restoring barrier function and stabilizing exposure. TFOS DEWS III treats inflammation as an etiological driver and recommends that its assessment inform severity, risk, and management. In this setting, short courses of topical corticosteroids (with intraocular pressure monitoring) provide rapid symptom/sign control, while T-cell-directed agents such as cyclosporine A and lifitegrast sustain immune modulation and support surface recovery.⁸⁹ Pharmacologic success in DED depends on achieving sustained, uniform surface exposure by tailoring formulation and posology to etiological drivers and adapting treatment over time.

5. Posology and its clinical relevance

5.1. Loading dose

In acute infections, a loading phase ensures that therapeutic concentrations are reached rapidly in the target tissue despite short ocular residence time. By preventing an initial window of subtherapeutic exposure, a loading dose also reduces the risk of early treatment failure and resistance selection.¹² In moderate to severe bacterial keratitis, current clinical protocols recommend antibiotics administered every

5–15 min during the first hour, then hourly, aligning with PK/PD principles of concentration- and exposure-dependent antibiotics (Fig. 3). This strategy supports attainment of class-specific targets such as C_{max}/MIC and AUC/MIC , optimizing early bactericidal activity and clinical response.^{95,96} Fortified formulations (e.g., tobramycin 14 mg/mL, cefazolin 50 mg/mL) are often employed when commercial preparations fail to achieve therapeutic concentrations in corneal tissue, particularly in severe bacterial keratitis. Compared to standard 0.3% tobramycin, fortified concentrations demonstrate a dose-proportional increase in tear film, stromal, and aqueous humor levels.⁹⁷ This enhanced bioavailability improves the likelihood of achieving PK/PD targets, especially for pathogens with higher MICs or in deep stromal involvement;⁹⁸ however, higher concentrations carry an increased risk of epithelial toxicity and delayed wound healing, particularly with aminoglycosides and amphotericin B.^{97,99} Moreover, when two fortified agents are administered in close succession, their hypertonicity can provoke reflex tearing and mechanical dilution of the first instilled drug, reducing its precorneal residence time and compromising effective exposure (i.e., washout effect).⁹⁸ Similarly, once microbial control has been achieved, topical corticosteroids are often introduced with an initial loading phase to ensure rapid suppression of ocular inflammation. Intensive early dosing (e.g., prednisolone acetate 1% every 1–2 h during the first 24–48 h) facilitates prompt tissue penetration and modulation of the inflammatory cascade.¹⁰⁰

5.2. Maintenance dose and tapering

Once therapeutic concentrations have been achieved, the purpose of maintenance dosing is to sustain drug levels within the therapeutic range, compensating for ongoing elimination while avoiding peaks that may induce toxicity.¹⁰¹

In bacterial keratitis, instillation frequency is typically reduced from hourly dosing to every 2 h for 24–48 h, then tapered every 2–3 days until a QID schedule is reached, which is generally maintained for 5–7 days before discontinuation. This stepwise strategy is applied consistently to both fortified antibiotic combinations and fluoroquinolone monotherapy.

This pattern, while broadly effective, can be further optimized by aligning maintenance and tapering schedules with the PK/PD index governing the drug's efficacy.¹⁰²

Topical corticosteroids follow a comparable principle of controlled dose reduction. After the initial intensive phase, topical corticosteroids

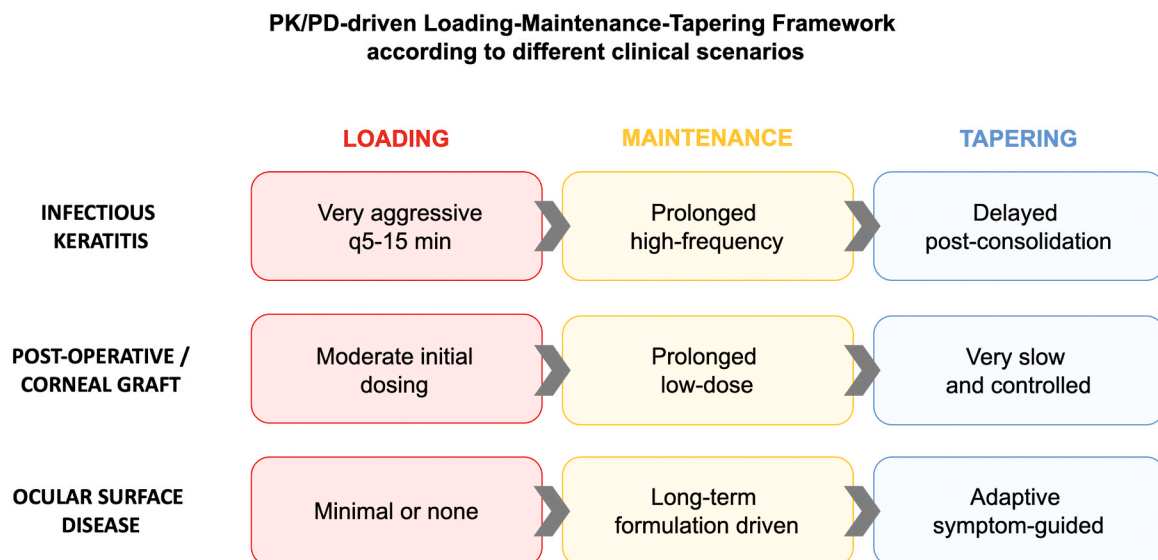


Fig. 3. PK/PD-driven loading-maintenance-tapering framework for topical ocular therapy across different clinical scenarios. The figure illustrates how dosing strategies can be adapted according to disease severity and treatment goals.

should be tapered in a controlled, stepwise manner to prevent rebound inflammation and minimize steroid-related adverse effects. The reduction schedule is guided by clinical improvement and epithelial healing, typically progressing from every 1–2 h to four times daily, then to twice or once daily over 1–2 weeks as inflammation resolves. Abrupt discontinuation should be avoided, as premature withdrawal may trigger recurrence of stromal inflammation.

For aminoglycosides, which exhibit concentration-dependent killing (Cmax/MIC), a high peak concentration during the loading phase is essential to achieve bactericidal activity.¹⁰³ Following this, dosing can typically be reduced more aggressively due to the post-antibiotic effect (PAE), a pharmacodynamic phenomenon wherein bacterial regrowth remains suppressed after drug concentrations fall below the MIC³². Although direct ocular evidence remains limited, this pharmacodynamic behavior allows for wider dosing intervals during the maintenance and tapering phases without compromising efficacy, if preceded by adequate early exposure.^{104,105}

For fluoroquinolones, which demonstrate AUC/MIC-dependent efficacy, the focus shifts to achieving sufficient cumulative exposure over time. As a result, dosing every 1–2 h is generally maintained for 24–48 h post loading to optimize bactericidal activity.¹⁰⁶ Because total exposure is the principal driver, tapering should be delayed until clinical improvement is consolidated, and sufficient cumulative dosing has occurred. Subtherapeutic tapering may risk underexposure, particularly for pathogens with higher MICs.^{107,108}

For β -lactams and glycopeptides, which are time-dependent ($T > MIC$), efficacy is closely tied to the duration drug concentrations remain above MIC during the dosing interval.¹⁰⁹ These agents lack a significant PAE, and subtherapeutic or missed doses, especially during nighttime, can result in transient periods of underexposure, which may not only compromise bacterial killing but also promote β -lactamase induction and selection of resistant strains.^{109,110} Hence, dosing should aim to maintain continuous exposure, including overnight instillations when feasible, and tapering should proceed cautiously.

These principles are broadly extensible to other antimicrobial classes with similar pharmacodynamic indices. Table 2 summarizes the major antibiotic classes used in ophthalmology, their PK/PD indices, and relevant clinical considerations.

5.3. Compliance and circadian factors

Once posology strategies are defined based on pharmacologic

principles, real-world factors, most notably patient adherence, become critical in ensuring therapeutic success.¹¹¹ In outpatient settings, adherence remains a major challenge, particularly during the maintenance and tapering phases, which often extend over days to weeks.¹¹² Frequent dosing schedules place a substantial burden on patients, especially older adults or those with reduced manual dexterity, visual impairment, or cognitive decline. Evidence indicates that nonadherence is closely associated with regimen complexity, difficulty in drop instillation, and medication-related discomfort.^{113,114}

Poor adherence may result from both intentional and unintentional factors: physical impediments (e.g., tremors, arthritis), forgetfulness, misinterpretation of instructions, or underestimation of disease severity. Nocturnal dosing is particularly problematic, as it disrupts sleep and may be neglected entirely. Moreover, repeated nighttime awakenings can exacerbate circadian misalignment, contributing to irregular sleep-wake cycles, reduced attention, mood disturbances, cognitive decline, and overall poorer quality of life, especially in older patients.¹¹⁵ Importantly, circadian rhythms regulate key ocular surface functions, including tear secretion, epithelial cell renewal, and immune response modulation, that are essential for maintaining homeostasis.¹¹⁶ Disruption of these rhythms may alter the ocular microenvironment, potentially influencing drug distribution, residence time, and therapeutic efficacy. To partially mitigate this, nighttime ointments or gel-forming drops may help maintain drug levels on the ocular surface and support adherence, although their pharmacokinetic limitations must be considered when designing regimens.¹¹⁷

Improving adherence requires a multifaceted approach. Patient education, simplification of regimens when possible, and individualized tapering based on clinical response and pathogen virulence are key. In select cases, caregiver involvement and the use of adherence aids, such as alarms or mobile app notifications, may improve compliance, especially in elderly or visually impaired patient.¹¹³

5.4. At-risk populations: physiological vulnerability, systemic exposure, and dosing considerations

Although topical ophthalmic therapies are intended to act locally, a substantial fraction of the instilled dose does not penetrate the eye and may be absorbed systemically through conjunctival and nasolacrimal pathways. As a result, dosing strategies in “at-risk” populations should account not only for local efficacy but also for age- and disease-related physiological factors that increase vulnerability to systemic exposure

Table 2

Summary of antimicrobial classes used in ocular therapy: PK/PD indices and clinical considerations.

Antibiotic Class	Mechanism of Action	PK/PD Index	Clinical Notes	Interaction Profile
Aminoglycosides (tobramycin, netilmicin)	Bactericidal. Inhibit protein synthesis by binding to 30S ribosomal subunit; cause misreading of mRNA	Cmax / MIC	High peak is key; post-antibiotic effect allows spacing after initial dose	Synergistic with beta-lactams
Beta-lactams (cefazolin, ceftazidime)	Bactericidal. Inhibit bacterial cell wall synthesis by binding penicillin-binding proteins (PBPs)	$T > MIC$	Efficacy relies on maintaining levels $> MIC$; avoid dosing gaps	Antagonism with bacteriostatic agents like macrolides or tetracyclines
Fluoroquinolones (moxifloxacin, levofloxacin)	Bactericidal. Inhibit DNA gyrase and topoisomerase IV, blocking DNA replication	AUC / MIC	Aim for good overall exposure; effective in mono- or combo-therapy	Neutral or synergistic with other bactericidals
Macrolides (azithromycin)	Bacteriostatic. Inhibit protein synthesis by binding to 50S ribosomal subunit	AUC / MIC	Long half-life permits infrequent dosing; not for acute keratitis	Antagonism with beta-lactams
Tetracyclines (doxycycline)	Bacteriostatic. Inhibit protein synthesis by binding to 30S ribosomal subunit	AUC / MIC	Adjunct in ocular surface inflammation; anti-collagenase and anti-inflammatory action	May antagonize bactericidal agents when combined
Glycopeptides (vancomycin)	Bactericidal. Inhibit cell wall synthesis by binding to D-Ala-D-Ala terminus of cell wall precursors	$T > MIC$	Aggressive dosing needed for resistant Gram-positive pathogens	Synergistic with aminoglycosides
Antifungals (natamycin, amphotericin B)	Fungicidal. Bind to ergosterol in fungal membranes, causing pore formation and cell death	Variable	Slow penetration: prolonged intensive treatment often required	May act synergistically with other antifungals
Antivirals (ganciclovir, trifluridine)	Inhibit viral DNA polymerase after phosphorylation, preventing DNA replication	Time-dependent	Sustained exposure needed; ganciclovir has lower toxicity	Usually used as monotherapy; few combination studies

and adverse effects.^{37,118}

In paediatric patients, anatomical and physiological factors amplify systemic exposure. Reduced tear volume, smaller ocular surface dimensions, and thinner, more permeable ocular membranes increase drug concentration at the ocular surface and facilitate absorption.¹¹⁹ Moreover, ophthalmic dosing is not weight-adjusted, resulting in a disproportionately high dose-to-body-mass ratio. PK modeling studies estimate that approximately one-half of the adult topical dose may be sufficient in neonates, increasing to about two-thirds by 3 years of age and approaching adult requirements by around 6 years.^{119,120} Importantly, infants are particularly vulnerable due to immature drug metabolism and incomplete blood–brain barrier development. Clinically relevant systemic adverse effects have been reported in children after topical ophthalmic administration, including central nervous system depression, sedation, and apnea with α 2-agonists and anticholinergic agents, as well as cardiovascular effects with topical β -blockers.¹¹⁸ From a dosing strategy perspective, these considerations support use of the lowest effective concentration, cautious dosing frequency, and avoidance of unnecessary polypharmacy. Simple administration measures, such as eyelid closure or nasolacrimal occlusion, have been shown to significantly reduce systemic absorption without compromising ocular efficacy.^{15,121}

In geriatric patients, reduced tear production and increased tear film instability occur within a context of ocular surface inflammaging characterized by chronic, low-grade inflammation and reduced tissue resilience.^{122,123} These changes may impair drug distribution and increase susceptibility to local toxicity, particularly with chronic topical therapy. Concomitant use of multiple topical agents further compromises tolerability and effective self-administration.¹²⁴ Systemic safety considerations are particularly relevant in geriatric patients due to frequent comorbidities and polypharmacotherapy, a setting associated with an increased risk of drug interactions.¹²⁵ Following topical ophthalmic administration, clinically meaningful systemic effects have been reported in older adults. Topical β -blockers may exacerbate bradycardia, hypotension, or bronchospasm, while centrally acting agents such as anticholinergics and α -agonists have been associated with confusion, sedation, and other central nervous system effects.^{118,126} From a dosing strategy perspective, this supports prioritizing tolerability, regimen simplification, and preservative-free formulations to maintain long-term adherence and minimize cumulative toxicity in older adults. Moreover, awareness of comorbidities that may increase susceptibility to specific drug classes should inform therapeutic choice and clinical monitoring.

Patients with renal or hepatic impairment represent an additional vulnerable group in topical ophthalmic therapy. In these patients, even limited systemic exposure may acquire clinical relevance due to reduced metabolic or excretory capacity, particularly during chronic treatment.^{126,127} In a nationwide population-based cohort study of patients with primary open-angle glaucoma and advanced chronic kidney disease, topical carbonic anhydrase inhibitor use was associated with a significantly increased risk of metabolic acidosis and progression to long-term dialysis.¹²⁸ In addition, several ophthalmic agents undergo hepatic metabolism following systemic absorption. Timolol represents a paradigmatic example, as it is predominantly cleared by hepatic CYP2D6, while ocular CYP2D6 expression is negligible. Consequently, reduced hepatic metabolic capacity or concomitant CYP2D6 inhibition may increase systemic exposure and the risk of cardiovascular and respiratory adverse effects.^{33,129} From a dosing strategy perspective, treatment in patients with renal or hepatic impairment should emphasize prudent agent selection, minimization of systemic exposure by avoiding excessive dosing frequency, and clinical monitoring.

6. Conclusions

Topical ocular therapy works best when dosing regimens match ocular PK and class specific PD. Loading, maintenance, and taper should be planned to overcome precorneal loss while avoiding toxicity.

Aminoglycosides need a high early peak then wider intervals using the post antibiotic effect, fluoroquinolones require sustained exposure for 24–48 h before taper, and beta lactams and glycopeptides need continuous time above MIC, including overnight when feasible. Clinical context further shapes schedules, with inflamed or infected eyes and suspected biofilm needing front loaded frequencies and sometimes fortified concentrations, post keratoplasty care requiring preservative free regimens and prolonged steroid taper with early steroid sparing agents, and dry eye benefiting from residence extending formulations that support adherence.

Promising directions include nanomedicine that codelivers immunosuppressants and antiangiogenic agents to prolong graft survival⁹⁸, and local delivery of regulatory T cells to reestablish immune tolerance in high-risk grafts, so far supported in animal models.¹³⁰ Additional priorities are stimuli responsive carriers, standardized ocular PK/PD targets, and adherence aware, circadian-aligned schedules tested in prospective trials.

6.1. Method of literature search

A comprehensive literature search was conducted between January and September 2025 to identify publications relevant to topical ocular pharmacology, ocular pharmacokinetics, and dosing regimens. The databases PubMed/MEDLINE, Embase, Scopus, and Cochrane Library were systematically searched without geographic restriction. The search strategy combined controlled vocabulary (MeSH and Emtree terms) and free-text keywords, including: ocular pharmacokinetics, topical ophthalmic drug delivery, pharmacodynamics, eye drops, ocular bioavailability, posology, ocular surface disease, corneal transplantation, antimicrobial therapy, nanomedicine, and ocular barriers. Boolean operators (AND/OR) were used to capture both experimental and clinical data.

Eligible studies included original research, clinical trials, pharmacokinetic or pharmacodynamic modelling papers, meta-analyses, and authoritative reviews published between 1980 and 2025 in English. Reference lists of key papers, consensus statements (e.g., TFOS DEWS, AAO PPP), and major ophthalmology textbooks were also manually screened to ensure completeness. Exclusion criteria were: (1) non-ophthalmic systemic pharmacology studies, (2) non-peer-reviewed materials, (3) animal studies without translational relevance, and (4) duplicate reports.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Luca Lucchino: Writing – original draft, Investigation, Data curation, Conceptualization. **Vito Romano:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Mariantonia Ferrara:** Writing – review & editing, Writing – original draft, Supervision, Methodology. **Lorenzo Drago:** Writing – review & editing, Methodology. **Ferdinando Giuliano:** Writing – original draft, Methodology. **Enrico Giuliano:** Writing – original draft, Methodology. **Francesco Semeraro:** Writing – review & editing, Supervision. **Riccardo Chiorrini:** Writing – original draft, Methodology.

Declaration of Competing 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.

Acknowledgements

None

Key references

Agrahari V, Mandal A, Agrahari V, Trinh HM, Joseph M, Ray A, Hadji H, Mitra R, Pal D, Mitra AK. A comprehensive insight on ocular pharmacokinetics. *Drug Deliv Transl Res*. 2016 Dec;6(6):735–754

This is one of the most authoritative modern reviews on ocular PK; it underpins the explanations of barriers, absorption routes, and bioavailability.

Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. *J Antimicrob Chemother*. 2005;55: 601–607.

This paper provides the foundational PK/PD indices ($T > MIC$, C_{max}/MIC , AUC/MIC) used to structure antimicrobial dosing principles.

62. Rhee MK, Ahmad S, Amescua G, Cheung AY, Choi DS, Jhanji V, Lin A, Mian SI, Viriya ET, Mah FS, Varu DM; American Academy of Ophthalmology Preferred Practice Pattern Cornea/External Disease Panel. Bacterial Keratitis Preferred Practice Pattern® . *Ophthalmology*. 2024 Apr;131(4):P87-P133

This is the main clinical practice guideline supporting the recommendations on loading doses, high-frequency regimens, and real-world antimicrobial posology.

References

- Lai SK, Wang YY, Hanes J. Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues. *Adv Drug Deliv Rev*. 2009 Nov;61(2):158–171.
- Ghosh S, Su YH, Yang CJ, Lai JY. Design of highly adhesive urchin-like gold nanostructures for effective topical drug administration and symptomatic relief of corneal dryness. *Small Struct*. 2025 Feb;6, 2400484.
- Lin HY, Wang SW, Mao JY, et al. Carbonized nanogels for simultaneous antibacterial and antioxidant treatment of bacterial keratitis. *Chem Eng J*. 2021 May;411, 128469.
- Luo LJ, Nguyen DD, Lai JY. Dually functional hollow ceria nanoparticle platform for intraocular drug delivery: a push beyond the limits of static and dynamic ocular barriers toward glaucoma therapy. *Biomaterials*. 2020 Jun;243, 119961.
- Yang CJ, Nguyen DD, Lai JY. Poly(l-histidine)-mediated on-demand therapeutic delivery of roughened ceria nanocages for treatment of chemical eye injury. *Adv Sci*. 2023 Sep;10, 2302174.
- Agrahari V, Mandal A, Agrahari V, et al. A comprehensive insight on ocular pharmacokinetics. *Drug Deliv Transl Res*. 2016 Dec;6(6):735–754.
- Ghate D, Edelhauser HF. Ocular drug delivery. *Expert Opin Drug Deliv*. 2006 Mar;3(2):275–287.
- Urtti A. Challenges and obstacles of ocular pharmacokinetics and drug delivery. *Adv Drug Deliv Rev*. 2006 Nov 15;58(11):1131–1135.
- Duvvuri S, Majumdar S, Mitra AK. Drug delivery to the retina: challenges and opportunities. *Expert Opin Biol Ther*. 2003 Feb;3(1):45–56. PMID:12718730.
- Dastjerdi MH, Sadrai Z, Saban DR, Zhang Q, Dana R. Corneal penetration of topical and subconjunctival bevacizumab. *Invest Ophthalmol Vis Sci*. 2011 Nov 7;52(12): 8718–8723.
- Baudouin C, Labbé A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res*. 2010 Jul;29(4): 312–334. <https://doi.org/10.1016/j.preteyeres.2010.03.001>.
- Delattre IK, Hites M, Laterre PF, et al. What is the optimal loading dose of broad-spectrum β -lactam antibiotics in septic patients? *Int J Antimicrob Agents*. 2020 Oct; 56(4), 106113.
- Healy DP, Holland EJ, Nordlund ML, et al. Concentrations of levofloxacin, ofloxacin, and ciprofloxacin in human corneal stromal tissue and aqueous humor after topical administration. *Cornea*. 2004 Apr;23(3):255–263.
- Kaye SB, Neal T, Nicholson S, et al. Concentration and bioavailability of ciprofloxacin and teicoplanin in the cornea. *Invest Ophthalmol Vis Sci*. 2009;50(7): 3176–3184. <https://doi.org/10.1167/iovs.08-3201>.
- Kaila T, Huupponen R, Salminen L. Effects of eyelid closure and nasolacrimal duct occlusion on the systemic absorption of ocular timolol in human subjects. *J Ocul Pharm*. 1986;2(4):365–369 (Fall).
- Hariprasad SM, Blinder KJ, Shah GK, et al. Penetration pharmacokinetics of topically administered 0.5% moxifloxacin ophthalmic solution in human aqueous and vitreous. *Arch Ophthalmol*. 2005;123(1):39–44. <https://doi.org/10.1001/archophth.123.1.39>.
- Ben Simon Cahane M, Barequet GJ, Grinbaum IS, et al. I. Human corneal stromal tissue concentration after consecutive doses of topically applied 3.3% vancomycin. *Br J Ophthalmol*. 2004 Jan;88(1):22–24. <https://doi.org/10.1136/bjo.88.1.22>.
- Spierer O, Regenbogen M, Lazar M, Yatziv Y. Effect of corneal thickness on the penetration of topical vancomycin. *Optom Vis Sci*. 2015 Oct;92(10):1027–1031.
- Kowalska-Krochmal B, Dudek-Wicher R. The minimum inhibitory concentration of antibiotics: methods, interpretation, clinical relevance. *Pathogens*. 2021 Feb 4;10(2):165.
- Herbert R, Caddick M, Somerville T, et al. Potential new fluoroquinolone treatments for suspected bacterial keratitis. *BMJ Open Ophthalmol*. 2022 Jul;7(1), e001002.
- Thomas RK, Melton R, Vollmer PM, Asbell PA. Vitro antibiotic resistance among bacteria from the cornea in the ARMOR study. *Optom Vis Sci*. 2021 Sep;98(9): 1113–1121.
- Sueke H, Kaye S, Neal T, et al. Minimum inhibitory concentrations of standard and novel antimicrobials for isolates from bacterial keratitis. *Invest Ophthalmol Vis Sci*. 2010 May;51(5):2519–2524.
- Dosler S, Hacıoglu M, Yilmaz FN, Oyari O. Biofilm modelling on the contact lenses and comparison of the in vitro activities of multipurpose lens solutions and antibiotics. *PeerJ*. 2020 Jun 24;8, e9419.
- Ishak A, Mazonakis N, Spornovasilis N, Akinosoglou K, Tsioutis C. Bactericidal versus bacteriostatic antibacterials: clinical significance, differences and synergistic potential in clinical practice. *J Antimicrob Chemother*. 2025 Jan 3;80(1): 1–17.
- Junaid Toluwalope, Wu Xuemei, Thanukrishnan Harisudhan, Venkataraman Raman. Chapter 30 - therapeutic drug monitoring. In: Dixon Thomas, ed. *Clinical Pharmacy Education, Practice and Research*. Elsevier; 2019:425–436.
- Armitage WJ, Goodchild C, Griffin MD, et al. High-risk corneal transplantation: recent developments and future possibilities. *Transplantation*. 2019 Dec;103(12): 2468–2478.
- Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. *J Antimicrob Chemother*. 2005;55:601–607.
- Meibohm B, Derendorf H. Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. *Int J Clin Pharm Ther*. 1997 Oct;35(10):401–413.
- Williams KA, Coster DJ. The immunobiology of corneal transplantation. *Transplantation*. 2007 Oct 15;84(7):806–813.
- Drusano GL, Preston SL, Owens RC, Jr, Ambrose PG. Fluoroquinolone pharmacodynamics. *Clin Infect Dis*. 2001;33(12):2091–2096.
- Owens Jr RC, Ambrose PG. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Infect Dis*. 2005;41(2):S127–S135.
- Zhanell GG, Craig WA. Pharmacokinetic contributions to postantibiotic effects. *Clin Pharm*. 1994 Nov;27(5):377–392.
- Nieminen T, Lehtimäki T, Mäenpää J, Ropo A, Uusitalo H, Kähönen M. Ophthalmic timolol: plasma concentration and systemic cardiopulmonary effects. *Scand J Clin Lab Invest*. 2007;67(2):237–245.
- Tomlinson A, Khanal S. Assessment of tear film dynamics: quantification approach. *Optic Surf*. 2005 Apr;3(2):81–95.
- Mochizuki H, Yamada M, Hato S, Nishida T. Fluorophotometric measurement of the precorneal residence time of topically applied hyaluronic acid. *Br J Ophthalmol*. 2008 Jan;92(1):108–111.
- Wu Z, Begley CG, Port N, Bradley A, Braun R, King-Smith E. The effects of increasing ocular surface stimulation on blinking and tear secretion. *Invest Ophthalmol Vis Sci*. 2015;56(8):4211–4220. <https://doi.org/10.1167/iovs.14-16313>.
- Del Amo EM. Topical ophthalmic administration: can a drug instilled onto the ocular surface exert an effect at the back of the eye? *Front Drug Deliv*. 2022;2, 954771. <https://doi.org/10.3389/fddv.2022.954771>.
- Mishima S, Gasset A, Klyce SD, Jr, Baum JL. Determination of tear volume and tear flow. *Invest Ophthalmol*. 1966 Jun;5(3):264–276.
- Jia T, Stapleton F, Iqbal F, et al. Comparison of eye drop retention time using fluorophotometry in three commercially available lubricant eye drops. *Optom Vis Sci*. 2024 Sep 1;101(9):603–607.
- Lanier OL, Manfre MG, Bailey C, et al. Review of approaches for increasing ophthalmic bioavailability for eye drop formulations. *AAPS PharmSciTech*. 2021 Mar 14;22(3):107.
- Angmo D, Wadhvani M, Velpandian T, Kotnal A, Sihota R, Dada T. Evaluation of physical properties and dose equivalency of generic versus branded latanoprost formulations. *Int Ophthalmol*. 2017 Apr;37(2):423–428.
- Garcia-Valdecabres M, López-Alemán A, Refojo MF. pH stability of ophthalmic solutions. *Optometry*. 2004 Mar;75(3):161–168.
- Chater PI, Wilcox MD, Pearson JP. Efficacy and safety concerns over the use of mucus modulating agents for drug delivery using nanoscale systems. *Adv Drug Deliv Rev*. 2018 Jan 15;124:184–192.
- Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. *World J Pharm*. 2013;2(2):47–64.
- Potvin R, Makari S, Rapuano CJ. Tear film osmolality and dry eye disease: a review of the literature. *Clin Ophthalmol*. 2015 Nov 2;9:2039–2047.
- Saettone MF, Salminen L. Ocular inserts for topical delivery. *Adv Drug Deliv Rev*. 1995;16(1):95–106.
- Davies NM. Biopharmaceutical considerations in topical ocular drug delivery. *Clin Exp Pharm Physiol*. 2000 Jul;27(7):558–562. <https://doi.org/10.1046/j.1440-1681.2000.03288.x>.
- Lallemant F, Schmitt M, Bourges JL, Gurny R, Benita S, Garrigue JS. Cyclosporine A delivery to the eye: a comprehensive review of academic and industrial efforts. *Eur J Pharm Biopharm*. 2017 Aug;117:14–28.
- Agarwal P, Craig JP, Rupenthal ID. Formulation considerations for the management of dry eye disease. *Pharmaceutics*. 2021 Feb 3;13(2):207.

50. Bairagi RD, Reon RR, Hasan MM, et al. Ocular drug delivery systems based on nanotechnology: a comprehensive review for the treatment of eye diseases. *Discov Nano*. 2025 May 3;20(1):75.
51. Gote V, Sikder S, Sicotte J, Pal D. Ocular drug delivery: present innovations and future challenges. *J Pharm Exp Ther*. 2019 Sep;370(3):602–624.
52. Zhou Y, Ma B, Liu Q, et al. Transmembrane protein CMTM6 alleviates ocular inflammatory response and improves corneal epithelial barrier function in experimental dry eye. *Invest Ophthalmol Vis Sci*. 2024 Jan 2;65(1):4.
53. Madhu C, Rix PJ, Shackleton MJ, Nguyen TG, Tang-Liu DD. Effect of benzalkonium chloride/EDTA on the ocular bioavailability of ketorolac tromethamine following ocular instillation to normal and de-epithelialized corneas of rabbits. *J Pharm Sci*. 1996 Apr;85(4):415–418.
54. Aguayo Bonniard A, Yeung JY, Chan CC, Birt CM. Ocular surface toxicity from glaucoma topical medications and associated preservatives such as benzalkonium chloride (BAK). *Expert Opin Drug Metab Toxicol*. 2016;12(11):1279–1289.
55. Brignole-Baudouin F, Riancho L, Liang H, Nakib Z, Baudouin C. vitro comparative toxicology of polyquad-preserved and benzalkonium chloride-preserved travoprost/timolol fixed combination and latanoprost/timolol fixed combination. *J Ocul Pharm Ther*. 2011;27(3):273–280.
56. Sarkar J, Chaudhary S, Namavari A, et al. Corneal neurotoxicity due to topical benzalkonium chloride. *Invest Ophthalmol Vis Sci*. 2012 Apr 6;53(4):1792–1802.
57. Jian HJ, Chiou YR, Anand A, et al. Carbon-in-carbon: hybrid carbonized nanomaterials with multifunctional activities for the treatment of endophthalmitis. *Chem Eng J*. 2024;491, 151997.
58. Yang CJ, Anand A, Huang CC, Lai JY. Unveiling the power of gabapentin-loaded nanoceria with multiple therapeutic capabilities for the treatment of dry eye disease. *ACS Nano*. 2023 Dec 26;17(24):25118–25135.
59. Luo LJ, Nguyen DD, Lai JY. Harnessing the tunable cavity of nanoceria for enhancing Y-27632-mediated alleviation of ocular hypertension. *Theranostics*. 2021 Mar 13;11(11):5447–5463.
60. Nguyen DD, Luo LJ, Lai JY. Dendritic effects of injectable biodegradable thermogels on pharmacotherapy of inflammatory glaucoma-associated degradation of extracellular matrix. *Adv Health Mater*. 2019 Dec;8(24), e1900702.
61. Rajan PB, Koilpillai J, Narayanasamy D. Advancing ocular medication delivery with nano-engineered solutions: a comprehensive review of innovations, obstacles, and clinical impact. *Cureus*. 2024 Aug 8;16(8), e66476.
62. Ghosh S, Yang CJ, Lai JY. Harnessing light: synthesis, mechanisms, and pre-clinical biomedical applications of stimuli-responsive multiscale composites. *Mater Today Bio*. 2025 Oct 21;35, 102442.
63. Ghosh S, Yang CJ, Lai JY. Hollow nanoarchitectures: materials engineering, nanochemistry, and biomedical applications. *Prog Mater Sci*. 2026;158, 101634.
64. Nguyen DD, Luo LJ, Yang CJ, Lai JY. Highly retina-permeating and long-acting resveratrol/metformin nanotherapeutics for enhanced treatment of macular degeneration. *ACS Nano*. 2023 Jan 10;17(1):168–183.
65. Paul S, Majumdar S, Chakraborty M, et al. In-situ gel bases ocular delivery system of Ganciclovir, in-vivo and in-vitro investigation. *BMC Pharm Toxicol*. 2025 May 13;26(1):102.
66. Unnikrishnan B, Lai JY, Anand A, Huang CC, Chang HT. Tiny tools, big vision: a mini-review on carbonized nanomaterials in ophthalmology. *J Control Release*. 2025 Dec 10;388(Pt 2), 114396.
67. Freddo TF. A contemporary concept of the blood-aqueous barrier. *Prog Retin Eye Res*. 2013 Jan;32:181–195.
68. Li S, Chen L, Fu Y. Nanotechnology-based ocular drug delivery systems: recent advances and future prospects. *J Nanobiotechnology*. 2023 Jul 22;21(1):232.
69. Austin A, Schallhorn J, Geske M, Mannis M, Lietman T, Rose-Nussbaumer J. Empirical treatment of bacterial keratitis: an international survey of corneal specialists. *BMJ Open Ophthalmol*. 2017 Aug;2(1).
70. Lee J, Pelis RM. Drug transport by the blood-aqueous humor barrier of the eye. *Drug Metab Dispos*. 2016 Oct;44(10):1675–1681.
71. Behlau I, Gilmore MS. Microbial biofilms in ophthalmology and infectious disease. *Arch Ophthalmol*. 2008 Nov;126(11):1572–1581.
72. Cursiefen C, Chen L, Dana MR, Streilein JW. Corneal lymphangiogenesis: evidence, mechanisms, and implications for corneal transplant immunology. *Cornea*. 2003 Apr;22(3):273–281.
73. Elder MJ, Stapleton F, Evans E, Dart JK. Biofilm-related infections in ophthalmology. *Eye (Lond)*. 1995;9(Pt 1):102–109.
74. Sharma S, Mohler J, Mahajan SD, et al. Microbial biofilm: a review on formation, infection, antibiotic resistance, control measures, and innovative treatment. *Microorganisms*. 2023 Jun 19;11(6):1614.
75. Liu HY, Prentice EL, Webber MA. Mechanisms of antimicrobial resistance in biofilms. *NPJ Antimicrob Resist*. 2024;2(1):27.
76. Mah TF, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. *Trends Microbiol*. 2001 Jan;9(1):34–39.
77. Cabrera-Aguas M, Chidi-Egboka N, Kandel H, Watson SL. Antimicrobial resistance in ocular infection: a review. *Clin Exp Ophthalmol*. 2024 Apr;52(3):258–275.
78. Luo Y, Yang Q, Zhang D, Yan W. Mechanisms and control strategies of antibiotic resistance in pathological biofilms. *J Microbiol Biotechnol*. 2021 Jan 28;31(1):1–7.
79. Brackman G, Coenye T. Quorum sensing inhibitors as anti-biofilm agents. *Curr Pharm Des*. 2015;21(1):5–11.
80. Choi V, Rohn JL, Stoodley P, et al. Drug delivery strategies for antibiofilm therapy. *Nat Rev Microbiol*. 2023;21:555–572. <https://doi.org/10.1038/s41579-023-00905-2>.
81. Lan Q, Deng Z, Li C, et al. Evaluation of hybrid capture-based targeted and metagenomic next-generation sequencing for pathogenic microorganism detection in infectious keratitis. *BMC Infect Dis*. 2025 Sep 29;25(1):1211.
82. Vajpayee RB, Sharma N, Sinha R, Agarwal T, Singhvi A. Infectious keratitis following keratoplasty. *Surv Ophthalmol*. 2007 Jan-Feb;52(1):1–12.
83. Di Tommaso C, Bourges JL, Valamanesh F, et al. Novel micelle carriers for cyclosporin A topical ocular delivery: in vivo cornea penetration, ocular distribution and efficacy studies. *Eur J Pharm Biopharm*. 2012 Jun;81(2):257–264.
84. Chatterjee S, Agrawal D. Use of topical cyclosporine 0.1% in therapeutic penetrating keratoplasty for fungal keratitis. *Cornea*. 2022;41(9):1116–1121.
85. Salabarria AC, Koch M, Schönberg A, et al. Topical VEGF-C/D inhibition prevents lymphatic vessel ingrowth into cornea but does not improve corneal graft survival. *J Clin Med*. 2020 Apr 28;9(5):1270.
86. Sharma N, Bagga B, Singhal D, et al. Fungal keratitis: a review of clinical presentations, treatment strategies and outcomes. *Ocul Surf*. 2022 Apr;24:22–30.
87. Keenan JD. Steroids in the management of infectious keratitis. *Cornea*. 2023;42(11):1333–1339.
88. Stapleton F, Argüeso P, Asbell P, et al. TFOS DEWS III: diagnostic methodology. *Am J Ophthalmol*. 2025 May 30;279:387–450.
89. Jones L, Craig JP, Markoulli M, et al. TFOS collaborator group. TFOS DEWS III: management and therapy. *Am J Ophthalmol*. 2025 Jun 2;279:289–386.
90. Stapleton F, Argüeso P, Asbell P, et al. TFOS DEWS III: digest. *Am J Ophthalmol*. 2025 Jun 4;279:451–553.
91. Gipson IK, Hori Y, Argüeso P. Character of ocular surface mucins and their alteration in dry eye disease. *Ocul Surf*. 2004 Apr;2(2):131–148.
92. Uchino Y. The ocular surface glycocalyx and its alteration in dry eye disease: a review. *Invest Ophthalmol Vis Sci*. 2018 Nov 1;59(14).
93. Pflugfelder SC, Farley W, Luo L, et al. Matrix metalloproteinase-9 knockout confers resistance to corneal epithelial barrier disruption in experimental dry eye. *Am J Pathol*. 2005 Jan;166(1):61–71.
94. Göbbels M, Spitznas M. Corneal epithelial permeability of dry eyes before and after treatment with artificial tears. *Ophthalmology*. 1992 Jun;99(6):873–878.
95. Rhee MK, Ahmad S, Amescua G, et al. Bacterial keratitis preferred practice pattern®. *Ophthalmology*. 2024 Apr;131(4):P87–P133.
96. Ung L, Chodosh J. Urgent unmet needs in the care of bacterial keratitis: an evidence-based synthesis. *Ocul Surf*. 2023 Apr;28:378–400.
97. Gilbert ML, Wilhelmus KR, Osato MS. Comparative bioavailability and efficacy of fortified topical tobramycin. *Invest Ophthalmol Vis Sci*. 1987 May;28(5):881–885.
98. Hanet MS, Jamart J, Chaves AP. Fluoroquinolones or fortified antibiotics for treating bacterial keratitis: systematic review and meta-analysis of comparative studies. *Can J Ophthalmol*. 2012 Dec;47(6):493–499.
99. Lin CP, Boehnke M. Effect of fortified antibiotic solutions on corneal epithelial wound healing. *Cornea*. 2000 Mar;19(2):204–206.
100. McGhee CN. Pharmacokinetics of ophthalmic corticosteroids. *Br J Ophthalmol*. 1992 Nov;76(11):681–684.
101. DeVane CL, Jusko WJ. Dosage regimen design. *Pharmacol & Ther*. 1982;17(2): 143–163. [https://doi.org/10.1016/0163-7258\(82\)90009-2](https://doi.org/10.1016/0163-7258(82)90009-2).
102. Scaglione F. Can PK/PD be used in everyday clinical practice. *Int J Antimicrob Agents*. 2002 Apr;19(4):349–353.
103. Gonzalez 3rd LS, Spencer JP. Aminoglycosides: a practical review. *Am Fam Physician*. 1998 Nov 15;58(8):1811–1820.
104. Krause KM, Serio AW, Kane TR, Connolly LE. Aminoglycosides: an Overview. *Cold Spring Harb Perspect Med*. 2016 Jun 1;6(6):a027029.
105. Scuderi AC, De Lazzari A, Miano F, Zola P. Residence time of netilmicin in tears. *Cornea*. 2002 Jan;21(1):48–50.
106. Drusano GL, Labro MT, Cars O, et al. Pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Microbiol Infect*. 1998 Apr;4 Suppl 2:S27–S41.
107. Blondeau JM. Fluoroquinolones: mechanism of action, classification, and development of resistance. *Surv Ophthalmol*. 2004 Mar;49(2):S73–S78.
108. Hooper DC. Emerging mechanisms of fluoroquinolone resistance. *Emerg Infect Dis*. 2001 Mar-Apr;7(2):337–341.
109. Turnidge JD. The pharmacodynamics of β -lactams. *Clin Infect Dis*. 1998;27(1): 10–22.
110. Poole K. Resistance to β -lactam antibiotics. *CMLS Cell Mol Life Sci*. 2004;61: 2200–2223.
111. Martin LR, Williams SL, Haskard KB, Dimatteo MR. The challenge of patient adherence. *Ther Clin Risk Manag*. 2005 Sep;1(3):189–199.
112. Khan M, Michelson S, Newman-Casey PA, Woodward MA. Medication adherence among patients with corneal diseases. *Cornea*. 2021 Dec 1;40(12):1554–1560.
113. Muñoz-Villegas P, Martínez-Bautista H, Olvera-Montano O. Determinants of adherence to treatment in patients with ophthalmic conditions. *Expert Rev Clin Pharm*. 2023 Jul-Dec;16(12):1249–1259.
114. Spencer SKR, Shulruf B, McPherson ZE, et al. Factors affecting adherence to topical glaucoma therapy: a quantitative and qualitative pilot study analysis in Sydney, Australia. *Ophthalmol Glaucoma*. 2019 Mar-Apr;2(2):86–93.
115. Murukesu RR, Alkaff ZA, Bridges C, Spitschan M. Ocular light exposure interventions for sleep, circadian rhythms, rest-activity cycles, mood, and cognitive function in older adults. *Cochrane Database Syst Rev*. 2025 Sep 12;9(9), CD016157.
116. Li L, Li H, Chen B. Chronobiological and neuroendocrine insights into dry eye. *Trends Mol Med*. 2025 Jun;31(6):522–534.
117. Al-Qaysi ZK, Beadham IG, Schwikard SL, Bear JC, Al-Kinani AA, Alany RG. Sustained release ocular drug delivery systems for glaucoma therapy. *Expert Opin Drug Deliv*. 2023;20(7):905–919.
118. Farkouh A, Frigo P, Czejka M. Systemic side effects of eye drops: a pharmacokinetic perspective. *Clin Ophthalmol*. 2016 Dec 7;10:2433–2441.
119. Batchelor HK, Marriott JF. Formulations for children: problems and solutions. *Br J Clin Pharm*. 2015 Mar;79(3):405–418.
120. Patton TF, Robinson JR. Pediatric dosing considerations in ophthalmology. *J Pediatr Ophthalmol*. 1976 May;13(3):171–178.

121. Müller L, Jensen BP, Bachmann LM, Wong D, Wells AP. New technique to reduce systemic side effects of timolol eye drops: the tissue press method—Cross-over clinical trial. *Clin Exp Ophthalmol*. 2020 Jan;48(1):24–30.
122. Di Zazzo A, Coassin M, Surico PL, Bonini S. Age-related ocular surface failure: a narrative review. *Exp Eye Res*. 2022 Jun;219, 109035. <https://doi.org/10.1016/j.exer.2022.109035>.
123. Perrie Y, Badhan RK, Kirby DJ, Lowry D, Mohammed AR, Ouyang D. The impact of ageing on the barriers to drug delivery. *J Control Release*. 2012 Jul 20;161(2): 389–398.
124. Kean EA, Adeleke OA. Geriatric drug delivery - barriers, current technologies and the road ahead. *J Drug Target*. 2024 Dec;32(10):1186–1206.
125. Diamond JP. Systemic adverse effects of topical ophthalmic agents. Implications for older patients. *Drugs Aging*. 1997 Nov;11(5):352–360. <https://doi.org/10.2165/00002512-199711050-00003>.
126. Vaajanen A, Vapaatalo H. A single drop in the eye - effects on the whole body? *Open Ophthalmol J*. 2017 Oct 31;11:305–314.
127. Urtti A, Salminen L. Minimizing systemic absorption of topically administered ophthalmic drugs. *Surv Ophthalmol*. 1993 May-Jun;37(6):435–456.
128. Wang YC, Ling XC, Tsai WH, Liu JS, Kuo KL. Risks of topical carbonic anhydrase inhibitors in glaucoma patients with chronic kidney disease. *Am J Ophthalmol*. 2023 Sep;253:49–55.
129. Volotinen M, Hakkola J, Pelkonen O, Vapaatalo H, Mäenpää J. Metabolism of ophthalmic timolol: new aspects of an old drug. *Basic Clin Pharm Toxicol*. 2011 May;108(5):297–303.
130. Shao C, Chen Y, Nakao T, et al. Local delivery of regulatory T cells promotes corneal allograft survival. *Transplantation*. 2019 Jan;103(1):182–190.