ISSN: 2456 - 530X
PubMed - National Library of Medicine - ID: 101737738

EIJO: Journal of Ayurveda, Herbal Medicine and Innovative Research (EIJO - AHMIR)
Einstein International Journal Organization (EIJO)
Available Online at: www.eijo.in
Volume – 11, Issue – 2, March – April – 2026, Page No. : 01 – 11

Stimuli-Responsive Nanoparticle Systems for Combination Drug Delivery in Ocular Infections

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Ocular infections represent a significant global health burden due to their potential to cause vision impairment and blindness if inadequately treated. Conventional ocular drug delivery systems suffer from poor bioavailability, rapid precorneal elimination, and limited penetration into ocular tissues. Recent advances in nanotechnology have enabled the development of stimuli-responsive nanoparticle systems that can release drugs in response to specific physiological or pathological triggers such as pH, temperature, enzymes, and light. These smart systems are particularly advantageous for combination drug delivery, allowing synergistic therapeutic effects, reduced dosing frequency, and minimized systemic side effects. This review provides a comprehensive overview of stimuli-responsive nanoparticles for ocular infections, focusing on their design, mechanisms, types of stimuli, and applications in delivering antimicrobial combinations. future perspectives are discussed to highlight their translational potential.

Keywords: Ocular Infections, Stimuli-Responsive Nanoparticles, Combination Drug Delivery, Smart Drug Delivery Systems, Nanotechnology, Controlled Release, Antimicrobial Therapy

Introduction

Ocular infections represent a significant global health burden and are among the leading causes of visual impairment and preventable blindness, particularly in developing countries. These infections can affect different anatomical regions of the eye, including the anterior segment (conjunctivitis and keratitis) and posterior segment (endophthalmitis), depending on the invading pathogen and route of infection. The causative agents are diverse, including bacteria (e.g., Staphylococcus aureus, Pseudomonas aeruginosa), fungi (e.g., Candida and Aspergillus species), viruses (e.g., herpes simplex virus), and parasites. Among these, bacterial and fungal infections are especially problematic due to their rapid progression, severity, and increasing resistance to conventional antimicrobial therapies.[1]

The treatment of ocular infections is inherently challenging due to the unique anatomical and physiological barriers of the eye. The corneal epithelium, with its tight junctions, acts as a major barrier to drug penetration, while the conjunctival epithelium allows only limited permeation. Additionally, precorneal factors such as tear turnover, reflex blinking, and nasolacrimal drainage significantly reduce the residence time of topically administered drugs. Consequently, conventional ocular formulations such as eye drops and ointments suffer from extremely low bioavailability, typically less than 5%,

requiring frequent dosing. This not only reduces patient compliance but also increases the risk of systemic absorption and associated side effects.[2]

In recent years, stimuli-responsive nanoparticles (SRNPs), also referred to as smart or intelligent drug delivery systems, have gained considerable attention. These systems are designed to respond to specific internal or external stimuli such as pH changes, temperature variations, enzymatic activity, redox gradients, or light exposure. Upon encountering these triggers, the nanoparticles undergo structural or physicochemical changes that result in controlled and site-specific drug release. In the context of ocular infections, pathological conditions often create a distinct microenvironment characterized by altered pH, elevated enzyme levels, and inflammatory mediators, which can be strategically exploited for targeted drug delivery.[3]

Simultaneously, combination drug therapy has become an increasingly important strategy in the management of ocular infections. The use of multiple therapeutic agents, such as antibiotics combined with anti-inflammatory drugs or antifungal agents with antioxidants, offers synergistic effects, enhances treatment efficacy, and reduces the emergence of drug resistance. However, delivering multiple drugs simultaneously in a controlled and effective manner remains a significant challenge using conventional delivery systems.[4]

This review aims to provide a comprehensive and critical overview of stimuli-responsive nanoparticle systems for combination drug delivery in ocular infections. It focuses on their design principles, mechanisms of action, types of stimuli, and therapeutic applications, while also addressing current challenges and future prospects in this rapidly evolving field.

Ocular Barriers and Challenges in Drug Delivery

The eye is a highly specialized and protected organ with unique anatomical and physiological features that maintain its structural integrity and function. While these protective mechanisms are essential for preserving vision, they also pose significant challenges for effective drug delivery. The presence of multiple static and dynamic barriers restricts drug penetration, reduces bioavailability, and limits therapeutic efficacy, particularly in the treatment of ocular infections. These barriers can be broadly classified into anatomical (static), physiological (dynamic), and biochemical barriers.[5]

1. Anatomical (Static) Barriers

Anatomical barriers are structural components of the eye that limit drug entry into ocular tissues.

1.1 Corneal Barrier

The cornea is the primary route for drug absorption following topical administration and consists of three major layers:

- **Epithelium**: The outermost layer with tight junctions, acting as a lipophilic barrier that restricts hydrophilic drug penetration.
- **Stroma**: A hydrophilic layer composed of collagen fibers, limiting the passage of lipophilic drugs.
- **Endothelium**: A relatively permeable inner layer that offers minimal resistance.

Due to this biphasic nature (lipophilic–hydrophilic–lipophilic), only drugs with balanced solubility can effectively permeate the cornea, making drug design and delivery highly challenging.[6]

1.2 Conjunctival Barrier

The conjunctiva covers a larger surface area than the cornea and is more permeable. However, its high vascularization leads to:

- Increased systemic absorption
- Reduced ocular bioavailability

This non-specific absorption decreases the amount of drug reaching intraocular tissues.

1.3 Blood-Aqueous Barrier (BAB)

The BAB is formed by tight junctions in the ciliary epithelium and iris blood vessels. It regulates the movement of substances from the bloodstream into the aqueous humor. This barrier:

- Restricts entry of systemically administered drugs
- Maintains ocular homeostasis[7]

1.4 Blood-Retinal Barrier (BRB)

The BRB consists of:

- Inner BRB: Formed by retinal capillary endothelial cells
- Outer BRB: Formed by retinal pigment epithelium (RPE)

2 Physiological (Dynamic) Barriers

Physiological barriers involve dynamic processes that actively remove or dilute drugs from the ocular surface.

2.1 Tear Film and Tear Turnover

The tear film (~7–10 µL volume) is continuously replenished, with a turnover rate of approximately 1–3 µL/min. Upon instillation of eye drops:

- Excess volume is rapidly drained
- Drug concentration decreases significantly

This leads to short precorneal residence time (1–2 minutes) and poor drug absorption.

2.2 Blinking Reflex

Blinking spreads the tear film and facilitates:

- Rapid elimination of instilled drugs
- Mechanical removal of formulations

2.3 Nasolacrimal Drainage

A significant portion of topically applied drugs is lost through the nasolacrimal duct into the nasal cavity, resulting in:

- Reduced ocular bioavailability
- Potential systemic side effects due to absorption through nasal mucosa.[8]

2.4 Efflux Mechanisms

Ocular tissues express efflux transporters such as P-glycoprotein (P-gp) and multidrug resistance proteins (MRPs) that actively pump drugs out of cells, limiting intracellular drug accumulation and therapeutic efficacy.9

3 Biochemical and Immunological Barriers

3.1 Enzymatic Degradation

The eye contains various metabolic enzymes (e.g., esterases, cytochrome P450 enzymes) that can degrade drugs before they reach their target site. This is particularly relevant for:

- Prodrugs
- Peptide-based therapeutics

3.2 Protein Binding

Drugs may bind to proteins present in the tear film or ocular tissues, reducing the free drug fraction available for therapeutic action.

3.3 Immune Defense Mechanisms

The eye possesses innate immune components such as:

- Lysozyme
- Lactoferrin
- Immunoglobulins

3.4 Barriers Specific to Posterior Segment Drug Delivery

Delivering drugs to the posterior segment (retina, vitreous humor) is particularly challenging due to:

- Limited permeability of BRB
- Vitreous humor viscosity
- Rapid clearance mechanisms

Topical and systemic routes are generally ineffective, necessitating invasive approaches such as intravitreal injections, which carry risks like retinal detachment and infection.[10]

3.5 Challenges in Conventional Ocular Drug Delivery

Despite various formulation strategies, conventional systems suffer from several limitations given in table 1 and Mechanism of Stimuli-Responsive Drug Release given in figure.1.[11,12]

Table 1: Various Challenges in Conventional Ocular Drug Delivery

Sn.	Challenge	Mechanism/Reason	Impact on Drug Delivery	Clinical Consequence
1	Low bioavailability	Rapid tear turnover, limited permeability	<5% of drug reaches intraocular tissues	Poor therapeutic efficacy
2	Rapid precorneal elimination	Tear dilution, blinking, nasolacrimal drainage	Short residence time (1–2 min)	Frequent dosing required
3	Corneal barrier	Tight junctions in epithelium restrict hydrophilic drugs	Limited drug permeation	Inadequate drug levels at target site
4	Conjunctival absorption	High vascularization of conjunctiva	Drug loss to systemic circulation	Reduced ocular availability
5	Blood-aqueous barrier (BAB)	Tight junctions in ciliary epithelium	Restricts systemic drug entry	Ineffective anterior segment therapy
6	Blood-retinal barrier (BRB)	Retinal endothelial & epithelial tight junctions	Prevents drug entry to posterior segment	Poor treatment of retinal infections
7	Efflux transporters	Presence of P-gp, MRPs	Active drug removal from cells	Reduced intracellular drug concentration

8	Enzymatic degradation	Esterases, proteases in tear fluid and tissues	Drug metabolism before absorption	Reduced drug stability and activity
9	Poor drug solubility	Many ocular drugs are hydrophobic	Limited dissolution in tear fluid	Low absorption and bioavailability
10	Limited retention time	Lack of mucoadhesion in conventional formulations	Rapid washout from ocular surface	Reduced therapeutic duration
11	Systemic absorption	Drainage through nasolacrimal duct	Drug enters systemic circulation	Side effects and toxicity
12	Protein binding	Interaction with tear proteins (albumin, lysozyme)	Reduced free drug concentration	Decreased pharmacological effect
13	Patient non-compliance	Frequent dosing schedules	Irregular drug administration	Treatment failure
14	Poor permeability to posterior segment	Limited diffusion through vitreous humor	Ineffective drug delivery to retina	Need for invasive methods
15	Formulation instability	pH, light, and temperature sensitivity	Drug degradation over time	Reduced shelf-life
16	Irritation and toxicity	Preservatives and high drug concentration	Ocular discomfort and inflammation	Reduced patient acceptance
17	Limited drug loading	Conventional dosage forms have low capacity	Insufficient therapeutic dose	Suboptimal treatment
18	Lack of targeted delivery	Non-specific distribution	Drug not concentrated at infection site	Reduced efficacy and increased side effects
19	Short half-life in ocular tissues	Rapid clearance mechanisms	Frequent re-administration needed	Poor patient adherence
20	Barrier to macromolecules	Large molecules cannot penetrate cornea	Ineffective delivery of biologics	Limits advanced therapies

3.6 Implications for Advanced Drug Delivery Systems

The complex interplay of these barriers necessitates the development of advanced drug delivery systems capable of:

- Prolonging precorneal residence time
- Enhancing corneal and conjunctival permeability
- Bypassing efflux mechanisms
- Protecting drugs from enzymatic degradation
- Providing targeted and controlled drug release.[12]

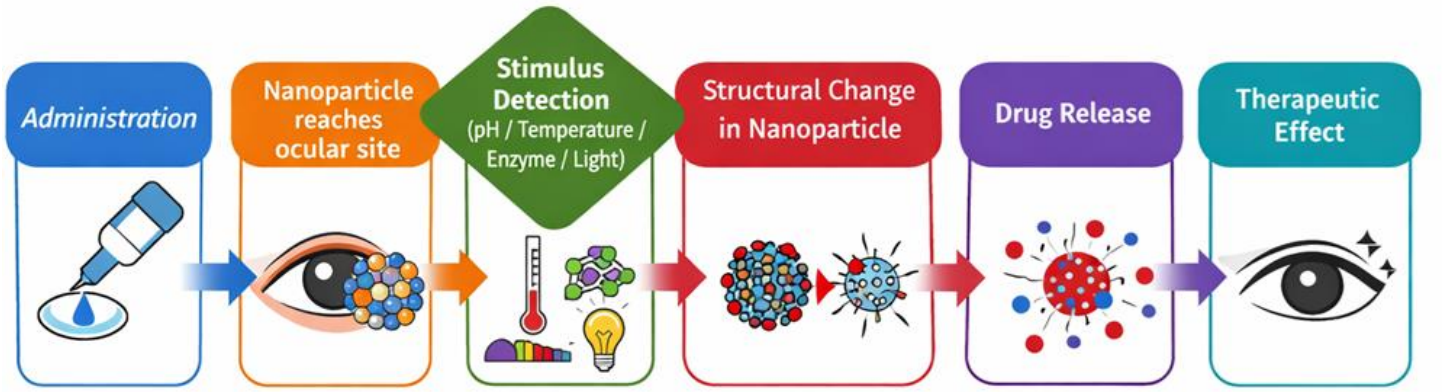

Figure1: Mechanism of Stimuli-Responsive Drug Release

4. Types of Stimuli-Responsive Systems

Stimuli-responsive nanoparticle systems are engineered to undergo physicochemical changes in response to specific internal (endogenous) or external (exogenous) stimuli. These systems enable site-specific, controlled, and sustained drug

release, making them highly suitable for ocular infections where micro-environmental conditions differ from normal tissues. Types of Stimuli-Responsive Systems and Their Mechanisms given in table 2.[14,15,]

4.1 pH-Responsive Systems

pH-responsive nanoparticles exploit variations in pH between healthy ocular tissues (neutral pH ~7.4) and infected or inflamed sites (slightly acidic pH ~5.5–6.8). These systems typically utilize polymers containing ionizable functional groups (e.g., carboxyl, amine), which undergo **protonation or deprotonation**, leading to:

- Swelling or shrinking of the nanoparticle matrix
- Disruption of polymer–drug interactions
- Triggered drug release

These systems are particularly effective for **bacterial and fungal infections**, where localized acidosis is common.[16]

4.2 Temperature-Responsive Systems

Temperature-responsive systems rely on polymers exhibiting Lower Critical Solution Temperature (LCST) or Upper Critical Solution Temperature (UCST) behavior. In ocular applications:

- Polymers remain soluble below LCST
- Undergo phase transition (gelation or collapse) above LCST

This property allows in situ gel formation and sustained drug release at physiological or inflamed temperatures. Common polymers include poly(N-isopropylacrylamide) (PNIPAAm) and poloxamers.

4.3 Enzyme-Responsive Systems

These systems are activated by enzymes that are overexpressed in infected or inflamed ocular tissues, such as:

- Lysozyme
- Matrix metalloproteinases (MMPs)
- Proteases

Nanoparticles are designed with enzyme-cleavable linkages, which undergo **enzymatic degradation**, leading to targeted drug release at infection sites.

4.4 Light-Responsive Systems

Light-responsive systems use external light (UV, visible, or near-infrared) as a trigger for drug release. Mechanisms include:

- Photochemical cleavage of bonds
- Photoisomerization
- Photothermal effects

Table 2: Types of Stimuli-Responsive Systems and Their Mechanisms[17]

Sn.	Stimulus Type	Trigger Mechanism	Materials/Polymers Used	Drug Release Mechanism	Applications in Ocular Infections	Advantages	Limitations
1	pH	Ionization of functional groups (–COOH, –NH_2) in acidic	Chitosan, Eudragit, poly(acrylic acid)	Swelling, polymer degradation, pore formation	Bacterial keratitis, fungal infections	Site-specific release, high sensitivity	Limited pH variation in some cases

		environment					
2	Temperature	LCST/UCST-based phase transition	PNIPAAm, Poloxamers, Pluronic F127	Sol–gel transition, polymer collapse	Sustained ocular delivery, post-surgical infections	Controlled release, improved retention	Risk of instability at fluctuating temperatures
3	Enzyme	Enzymatic cleavage of polymer backbone or linkers	Peptide-based polymers, gelatin, dextran	Degradation of nanoparticle matrix	Infection targeting, inflammation-mediated release	High specificity, targeted delivery	Enzyme variability among patients
4	Light	Photochemical bond cleavage or photothermal effect	Gold nanoparticles, azobenzene polymers	Light-triggered structural disruption	Controlled ocular drug delivery	Precise spatial and temporal control	Limited tissue penetration, potential phototoxicity
5	Redox (additional)	Glutathione-mediated disulfide bond cleavage	Disulfide-linked polymers, PEG derivatives	Reduction-triggered nanoparticle breakdown	Intracellular drug delivery	High intracellular specificity	Limited extracellular applicability
6	Magnetic (additional)	External magnetic field guidance	Iron oxide nanoparticles	Magnetically guided accumulation and release	Targeted ocular delivery	Non-invasive targeting	Requires external device
7	Multi-stimuli	Combination of pH, temperature, enzyme	Hybrid polymers	Sequential or dual-trigger release	Complex infections (biofilms)		

5. Nanoparticle Systems for Combination Drug Delivery

Nanoparticle-based drug delivery systems have significantly improved ocular therapeutics by enabling simultaneous delivery of multiple drugs**,** enhanced bioavailability, and targeted action. These systems are particularly useful in ocular infections for co-delivering antimicrobial, anti-inflammatory, and antioxidant agents, resulting in synergistic therapeutic effects**.** An ideal system should be biocompatible, mucoadhesive, and capable of controlled drug release while overcoming ocular barriers. Nanocarriers for Combination Drug Delivery in Ocular Infections is given in table 3. and some applications also in given in table 4.[18,19]

5.1 Liposomes

Liposomes are phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic drugs. They offer excellent biocompatibility and can be surface-modified for targeted delivery.

Effective for dual-drug delivery (e.g., antibiotic + anti-inflammatory).

5.2 Polymeric Nanoparticles

These are biodegradable systems (e.g., PLGA, chitosan) providing controlled and sustained drug release with enhanced mucoadhesion and drug protection.

Suitable for prolonged and combination therapy.

5.3 Solid Lipid Nanoparticles (SLNs)

SLNs consist of solid lipid matrices that improve drug stability and enable controlled release. Best for lipophilic drug combinations, though loading capacity is limited.

5.4 Nano-emulsions

Nano-emulsions are oil–water dispersions with high surface area, enhancing drug absorption and ocular penetration. Ideal for hydrophobic drugs, especially antifungal and antibacterial agents.

Table 3: Nanocarriers for Combination Drug Delivery in Ocular Infections[20,21]

Sn.	Nanocarrier	Composition/Structure	Drug Loading Capability	Advantages	Limitations	Applications in Ocular Infections
1	Liposomes	Phospholipid bilayer vesicles	Hydrophilic + Lipophilic drugs	Biocompatible, dual drug loading, targeted delivery, reduced toxicity	Physical instability, leakage, high production cost	Bacterial keratitis, conjunctivitis, endophthalmitis
2	Polymeric Nanoparticles	PLGA, chitosan, alginate matrices	High, both single & multiple drugs	Controlled release, mucoadhesion, protection from degradation	Complex synthesis, possible polymer toxicity	Sustained antimicrobial delivery, chronic infections
3	Solid Lipid Nanoparticles (SLNs)	Solid lipid core + surfactant	Mainly lipophilic drugs	High stability, controlled release, improved drug protection	Limited drug loading, drug expulsion during storage	Fungal keratitis, anti-inflammatory delivery
4	Nanoemulsions	Oil-in-water or water-in-oil systems	High for hydrophobic drugs	Enhanced penetration, ease of preparation, improved bioavailability	Short shelf-life, surfactant-related irritation	Antifungal and antibacterial therapy
5	Nanostructured Lipid Carriers (NLCs)	Solid + liquid lipid mixture	Higher than SLNs	Improved drug loading, reduced drug expulsion	Complex formulation	Advanced lipid-based ocular delivery
6	Dendrimers	Highly branched polymers	High (surface functionalization)	Precise drug targeting, multivalent interactions	Toxicity concerns, expensive synthesis	Targeted antimicrobial delivery
7	Polymeric Micelles	Amphiphilic block copolymers	Hydrophobic drugs	Solubilization of poorly soluble drugs, small size	Limited stability in dilution	Delivery of antifungal drugs
8	Nanogels	Crosslinked hydrophilic polymer networks	High (hydrophilic drugs)	High water content, biocompatibility, stimuli-responsive	Mechanical weakness	Controlled ocular drug delivery
9	Hybrid Nanoparticles	Combination of polymer + lipid	Dual drug loading	Improved stability and functionality	Complex design	Multi-drug ocular therapy
10	Metallic Nanoparticles	Gold, silver nanoparticles	Surface adsorption	Antimicrobial properties, photothermal effects	Potential toxicity	

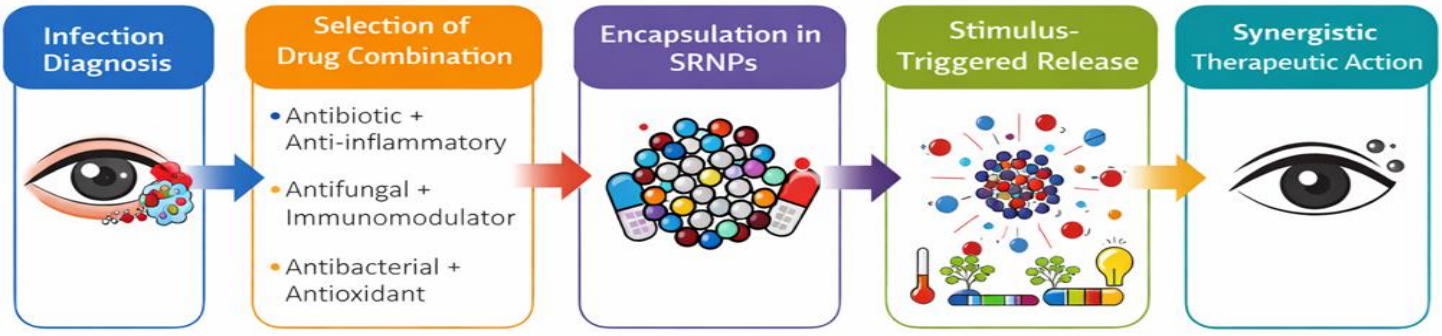

Figure 2; Combination Therapy approach

Table 4: Applications of Stimuli-Responsive Nanoparticles (SRNPs) in Ocular Infections [22,23]

Sn.	Disease/Condition	Type of Infection	Drug Combination	Nanocarrier/System Used	Stimulus Type	Therapeutic Outcome	Advantages Achieved
1	Bacterial Keratitis	Bacterial (Pseudomonas, Staphylococcus)	Antibiotic + Anti-inflammatory (e.g., Ciprofloxacin + Dexamethasone)	Polymeric nanoparticles, liposomes	pH / Enzyme	Reduced inflammation, enhanced bacterial eradication	Sustained release, improved corneal penetration
2	Fungal Keratitis	Fungal (Candida, Aspergillus)	Antifungal + Immunomodulator (e.g., Natamycin + Cyclosporine)	SLNs, nanoemulsions	pH / Temperature	Improved drug solubility and antifungal activity	Enhanced bioavailability, reduced toxicity
3	Conjunctivitis	Bacterial/Viral	Dual antibiotics (e.g., Tobramycin + Moxifloxacin)	Nanoemulsions, polymeric NPs	pH / Enzyme	Faster infection clearance	Reduced dosing frequency, better compliance
4	Endophthalmitis	Severe intraocular infection	Antibiotic + Antioxidant (e.g., Vancomycin + Vitamin E)	Liposomes, hybrid nanoparticles	Enzyme / Redox	Enhanced therapeutic efficacy and retinal protection	Targeted delivery to posterior segment
5	Uveitis (Infectious/Inflammatory)	Inflammatory condition	Steroid + Immunosuppressant	Polymeric nanoparticles, nanogels	Temperature / pH	Reduced inflammation and immune response	Sustained drug release, reduced side effects
6	Corneal Ulcer	Bacterial/Fungal	Antibiotic + Growth factor	Chitosan-based nanoparticles	Enzyme-responsive	Accelerated wound healing	Enhanced tissue regeneration
7	Viral Keratitis	Viral (HSV)	Antiviral + Anti-inflammatory (e.g., Acyclovir + Steroid)	Liposomes, dendrimers	pH / Enzyme	Reduced viral load and inflammation	Improved drug targeting
8	Dry Eye with Infection	Secondary infection	Lubricant + Antibiotic	Nanoemulsion, nanogels	Temperature	Improved hydration and infection control	Increased retention time
9	Biofilm-associated infections	Chronic bacterial infection	Antibiotic + Anti-biofilm agent	Hybrid nanoparticles	Multi-stimuli	Disruption of biofilm and improved drug penetration	Overcomes drug resistance
10	Post-surgical ocular infection	Mixed microbial infection	Broad-spectrum antibiotic + Anti-inflammatory	SLNs, polymeric nanoparticles	Temperature / pH		

Future Perspectives

Stimuli-responsive nanoparticle systems hold great promise for advancing ocular drug delivery. Future developments include integration with **gene therapy** for targeted genetic treatment and the adoption of **personalized medicine** to tailor therapies based on individual patient needs. The emergence of multi-stimuli-responsive smart biomaterials will enable more precise and controlled drug release. Advances **in** biodegradable and biocompatible polymers will improve safety and reduce toxicity. Additionally, combining nanotechnology with artificial intelligence and biosensors may allow real-time monitoring and on-demand drug delivery. Efforts in scalable manufacturing and regulatory standardization will further support clinical translation. Overall, these innovations are expected to significantly enhance therapeutic outcomes in ocular diseases.[24]

Conclusion

Stimuli-responsive nanoparticle systems represent a transformative approach in the field of ocular drug delivery, particularly for the management of infectious diseases. These advanced systems effectively address the limitations of conventional formulations by enhancing drug bioavailability, prolonging precorneal residence time, and enabling targeted delivery. The integration of combination drug therapy within nanoparticle platforms further improves therapeutic outcomes through synergistic action and reduced drug resistance. Various nanocarriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions have demonstrated significant potential in delivering multiple drugs efficiently. The ability of these systems to respond to internal and external stimuli, including pH, temperature, enzymes, and light, allows precise control over drug release at the site of infection. This targeted and controlled release minimizes systemic side effects and improves patient compliance. Moreover, advancements in characterization techniques ensure the development of stable, safe, and effective formulations. Continued research and technological innovations are essential to overcome these limitations. Future perspectives include the development of multi-stimuli-responsive and personalized drug delivery systems.

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