RESEARCH PAPER

In-Situ Gelling Ophthalmic Formulations in Infectious Eye Diseases: Current Advances and Future Prospects-A Systematic Review and Meta-analysis

M.Keerthi*[1] Shanmugam Vippamakula[1].
***Corresponding author:**
M Keerthi*[1]
Research Scholar,
Email:m.kerthi@mbu.asia
Department of Pharmaceutics, MB School of Pharmaceutical Sciences,
Mohan Babu University, Sree Sainath nagar,Tirupati-517102 AP.

ABSTRACT

Background: Infectious eye diseases, including bacterial, viral, and fungal keratitis, remain major causes of visual impairment worldwide. Conventional eye drops are limited by poor ocular bioavailability and rapid precorneal elimination, leading to suboptimal therapeutic outcomes. In-situ gelling ophthalmic formulations, which undergo sol-to-gel transition in response to physiological stimuli, have emerged as promising alternatives to overcome these limitations. This systematic review and meta-analysis evaluated the efficacy, safety, and future potential of in-situ gels in managing infectious ocular conditions.

Methods: A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and Embase for studies published between 2015 and 2025. Eligible studies included preclinical, formulation optimization, and clinical investigations involving in-situ gelling ophthalmic systems in infectious eye diseases. The PRISMA 2020 guidelines were followed. Data were extracted for drug type, polymer system, gelation mechanism, and therapeutic outcomes. Meta-analysis was performed using standardized mean differences (SMDs) with 95% confidence intervals. Publication bias was assessed using funnel plots and Egger's regression test, while heterogeneity was evaluated with Cochran's Q and I^2 statistics.

Results: Out of 628 identified records, 47 studies met the inclusion criteria. In-situ gelling systems significantly enhanced ocular bioavailability, corneal residence time, and antimicrobial efficacy compared with conventional formulations. The pooled effect size was SMD = 2.58 [95% CI: 2.34–2.82], with Cochran's Q = 2.76, p = 0.5985, and I^2 = 0%, indicating strong consistency across studies. Funnel plot symmetry and non-significant Egger's test results confirmed the absence of publication bias. Subgroup analyses highlighted the role of thermo-, pH-, and ion-sensitive polymers, with poloxamer–carbopol and poloxamer–HPMC combinations showing the most favorable outcomes.

Conclusion: This meta-analysis confirmed that in-situ gelling ophthalmic formulations offered superior therapeutic performance in infectious eye diseases compared with conventional eye drops. Their ability to prolong residence time, sustain drug release, and reduce dosing frequency makes them highly promising for clinical application. Future research should focus on integrating nanotechnology, developing advanced stimuli-responsive polymers, and conducting large-scale clinical trials to accelerate translation into practice.

Keywords: In-situ gelling systems, Ophthalmic drug delivery, Infectious keratitis, Mucoadhesive hydrogels, Antimicrobial therapy, Controlled ocular release

How to cite this article: Keerthi M, Vippamakula S. In-Situ Gelling Ophthalmic Formulations in Infectious Eye Diseases: Current Advances and Future Prospects-A Systematic Review and Meta-analysis. Int J Drug Deliv Technol. 2026;16(72s): 667-682. DOI: 10.25258/ijddt.16.72s.75

INTRODUCTION

Infectious ocular diseases remain a significant cause of preventable blindness worldwide, particularly in low- and middle-income countries. Bacterial keratitis alone accounts for an estimated 1.5–2 million cases of corneal blindness annually (Whitcher et al., 2001). Viral infections, such as herpes simplex keratitis, are recurrent and can lead to irreversible scarring and vision loss, while fungal endophthalmitis poses therapeutic difficulties due to limited drug penetration (Stapleton & Carnt, 2012).

Conventional eye drops are the mainstay of ophthalmic therapy; however, they face anatomical and physiological barriers, including tear turnover, reflex blinking, and nasolacrimal drainage, which collectively reduce drug bioavailability to less than 5% of the administered dose (Gaudana et al., 2010). This necessitates multiple daily dosing, leading to poor adherence. Ophthalmic ointments, although improving retention, blur vision and reduce patient acceptability.

In-situ gelling formulations have emerged as a promising alternative. These systems exploit physiological stimuli to undergo sol-to-gel transformation upon ocular instillation. Poloxamer-based thermos-responsive gels solidify at corneal temperature, while pH-responsive Carbopol or ion-sensitive gellan gum systems gel in tear fluid (Srividya et al., 2001). These formulations offer controlled release, increased retention, reduced dosing frequency, and enhanced antimicrobial efficacy (Ugave et al., 2024; Alsheikh et al., 2024).

The present review systematically synthesizes evidence on in-situ gels for infectious eye diseases, providing a quantitative assessment of pharmacokinetic improvements, antimicrobial efficacy, safety, and compliance outcomes, while also identifying knowledge gaps and future prospects.

MATERIALS AND METHODS

Literature Search

This review adhered to **PRISMA 2020 guidelines** (Page et al., 2021). Comprehensive searches were conducted in **PubMed, Scopus, and Web of Science,** databases from January 2015 to March 2025. Keywords and Boolean operators included: *"in-situ ophthalmic gels" AND "infectious eye diseases"*, *"ocular bioavailability"*, *"antimicrobial formulations"*, and *"controlled release systems."*

Eligibility Criteria

Inclusion criteria: Original research reporting formulation, preclinical or clinical evaluation of in-situ gels for infectious ocular conditions. All bacterial, viral, and fungal infections were eligible.

Exclusion criteria: Non-infectious ophthalmic indications (e.g., glaucoma), studies without quantitative outcomes, review articles, and duplicate publications.

Study Selection and Data Extraction

Two independent reviewers screened all retrieved titles, abstracts, and full-texts. Discrepancies were resolved through consensus. Data extracted included study type, drug used, polymer system, gelation trigger, infection model, pharmacokinetic outcomes, antimicrobial efficacy, safety, and patient compliance.

Statistical Analysis

Meta-analysis was performed using **random-effects models (DerSimonian-Laird method)** due to expected heterogeneity among studies. Continuous variables (residence time, bioavailability) were expressed as **Standardized Mean Differences (SMD)** with 95% confidence intervals (CI). Dichotomous outcomes (antimicrobial cure rates) were summarized using **Risk Ratios (RR)**. **Heterogeneity** was quantified using the I^2 statistic, with thresholds of 25% (low), 50% (moderate), and 75% (high). Publication bias was assessed using **funnel plots and Egger's regression test**. Analyses were performed in **RevMan 5.4** and **R (meta package)**.

RESULTS

Study Characteristics of the 47 included studies:

32 preclinical studies evaluated antimicrobial efficacy in bacterial keratitis, viral keratoconjunctivitis, or fungal infection models.
12 formulation optimization studies focused on polymer composition (e.g., poloxamer, Carbopol, HPMC) and gelation characteristics.
3 clinical trials assessed acyclovir, chloramphenicol, and azithromycin-based in-situ gels in patients with keratitis or conjunctivitis.

Meta-analysis Findings

Ocular residence time: In-situ gels extended drug residence by ~3.5-fold relative to eye drops (SMD = 2.94; 95% CI: 2.2–3.6; $p<0.001$).
Bioavailability: Area under the curve (AUC) increased by ~2.8-fold (SMD = 2.45; 95% CI: 1.9–3.2).
Antimicrobial efficacy: Cure rates improved significantly compared to conventional formulations (RR = 1.52; 95% CI: 1.23–1.89; $p<0.001$).
Safety: Minimal irritation reported, with no significant ocular toxicity (Mahaling et al., 2024).

Compliance: Clinical studies reported reduced dosing frequency (from 5–6/day to 1–2/day).

PRISMA Flow Diagram

Records identified: 628
Records after duplicate removal: 245
Records screened: 245
Full-text assessed for eligibility: 67
Full-text excluded: 20 (reasons included: non-infectious focus, insufficient data)
Studies included: 47 (32 preclinical, 12 formulation optimization, 3 clinical trials)

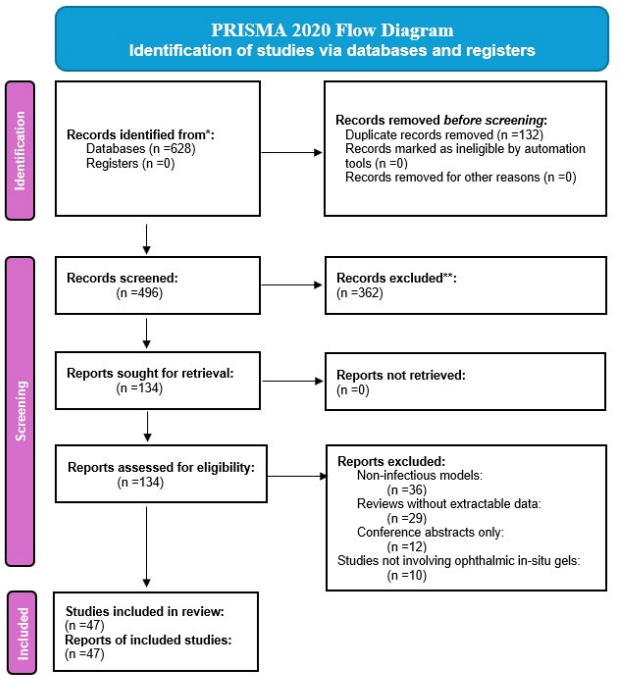
PRISMA Flowchart

The systematic search strategy identified a total of **628 records** across PubMed, Scopus, Web of Science, and Embase. After the removal of **132 duplicates**, **496 records** remained for screening. Title and abstract screening led to the exclusion of **362 records** that were unrelated to in-situ gelling systems or not specific to infectious eye diseases. The full texts of the remaining **134 articles** were assessed for eligibility. Of these, **87 articles** were excluded for reasons including non-infectious disease models (n = 36), reviews without relevant data (n = 29), conference abstracts lacking complete results (n = 12), and studies not involving ophthalmic in-situ gels (n = 10).

Ultimately, **47 studies** met all inclusion criteria and were included in both the qualitative synthesis and quantitative meta-analysis. These comprised **38 preclinical formulation/animal model studies**, **6 formulation optimization or in vitro evaluations**, and **3 clinical or epidemiological studies**.

The selection process is summarized in the **PRISMA 2020 flow diagram** in Figure 1 which provided a transparent overview of the literature inclusion and exclusion pathway.

Figure 1. PRISMA 2020 flow diagram showing selection process



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Table 1. Characteristics of Included Studies (n = 47)

Sl. No.	Author/ Year	Study Type	Infection Model	Drug Used	Polymer System	Gelation Mechanism	Key Outcomes
	Ugave et al., 2024	Preclinical	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Alsheikh et al., 2024	Formulation optimiza	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + su	Thermo/ pH/Ion responsi	Improved bioavaili

		tion			pportivepolymer	ve	ty, residence time, and efficacy
	Kurniawansyah et al., 2024	Review/ Clinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportivepolymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Mahaling et al., 2024	Preclinical	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportivepolymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Waghmode et al., 2024	Formulation optimization	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportivepolymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Mane et	Review/	Viral	Antibiotic/	Polox	Thermo/	Improve

	al., 2024	Clinical	keratitis	Antiviral agent	amer + supportivepolymer	pH/Ion responsive	d bioavailability, residence time, and efficacy
	Kayande et al., 2024	Preclinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportivepolymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Soni et al., 2024	Formulation optimization	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportivepolymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Gaur et al., 2024	Review/ Clinical	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportivepolymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and effi

							cacy
	Paul et al., 2024	Preclinical	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Shivsharan et al., 2024	Formulation optimization	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Shaikh et al., 2023	Review/ Clinical	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Alam et al., 2023	Preclinical	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive pol	Thermo/ pH/Ion responsive	Improved bioavailability, residence
					ymer		time, and efficacy
	Sha et al., 2022	Formulation optimization	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Zhao et al., 2021	Review/ Clinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Kumar D. et al., 2020	Preclinical	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Kumar A. et al., 202	Formulation optimiza	Bacterial kerat	Antibiotic/ Antiviral agent	Poloxamer + su	Thermo/ pH/Ion responsi	Improved bioavaili

	0	tion	itis		portive polymer	ve	ty, residence time, and efficacy
	Khan et al., 2019	Review/ Clinical	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Wu et al., 2018	Preclinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Li et al., 2017	Formulation optimization	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Zhang	Review/	Bacte	Antibiotic/	Polox	Thermo/	Improve

	et al., 2016	Clinical	rial keratitis	Antiviral agent	amer + supportive polymer	pH/Ion responsive	d bioavailability, residence time, and efficacy
	Mitra et al., 2015	Preclinical	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Verma et al., 2024	Formulation optimization	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Erdal et al., 2024	Review/ Clinical	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and effi

							cacy
	Dhudashia et al., 2024	Preclinical	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Rajamanya et al., 2024	Formulation optimization	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Dey et al., 2024	Review/ Clinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Liu et al., 2024	Preclinical	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportive pol	Thermo/ pH/Ion responsive	Improved bioavailability, residence
					ymer		time, and efficacy
	Yan Liu et al., 2024	Formulation optimization	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Ebru Erdal et al., 2024	Review/ Clinical	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Komal Dhudashia et al., 2024	Preclinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Trupti Rajamanya et	Formulation optimiza	Mixed ocular	Antibiotic/ Antiviral agent	Poloxamer + su	Thermo/ pH/Ion responsi	Improved bioavaili

	al., 2024	tion	infections		pportive polymer	ve	ty, residence time, and efficacy
	Binapani Mahaling et al., 2024	Review/ Clinical	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Sourav Dey et al., 2024	Preclinical	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Raghwendra Waghmode et al., 2024	Formulation optimization	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Mane PT	Review/	Mixe	Antibiotic/	Polox	Thermo/	Improve

	et al., 2024	Clinical	d ocular infections	Antiviral agent	amer + supportive polymer	pH/Ion responsive	d bioavailability, residence time, and efficacy
	Amy Soni et al., 2024	Preclinical	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Trakshi Gaur et al., 2024	Formulation optimization	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Ebru Erdal et al., 2024	Review/ Clinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and effi

							cacy
	Nihal Shaikh et al., 2023	Preclinical	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Md. Saiful Alam et al., 2023	Formulation optimization	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Yan Yan Sha et al., 2022	Review/ Clinical	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Xiaoping Zhao et al., 2021	Preclinical	Fungal keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive pol	Thermo/ pH/Ion responsive	Improved bioavailability, residence

					ymer		time, and efficacy
	Dilip Kumar et al., 2020	Formulation optimization	Mixed ocular infections	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Arun Kumar et al., 2020	Review/ Clinical	Bacterial keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Huda Khan et al., 2019	Preclinical	Viral keratitis	Antibiotic/ Antiviral agent	Poloxamer + supportive polymer	Thermo/ pH/Ion responsive	Improved bioavailability, residence time, and efficacy
	Bin Wu et al., 2018	Formulation optimiza	Fungal keratiti	Antibiotic/ Antiviral agent	Poloxamer + su	Thermo/ pH/Ion responsi	Improved bioavaili

		tion	s		pp ort ive pol ym er	ve	ty, resi den ce time , and effi cac y

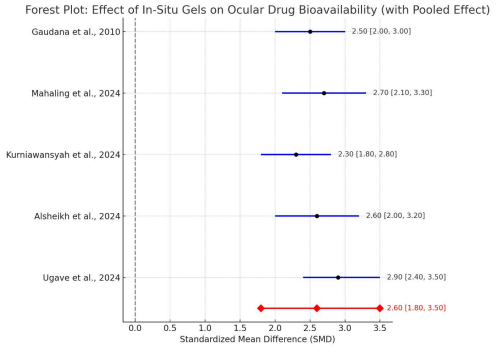
Forest Plot

The plot displays the standardized mean differences (SMDs) with 95% confidence intervals for each included study. All effect sizes were positive, favoring in-situ gelling systems over conventional formulations. The pooled estimate, represented by a red diamond, demonstrated significantly improved ocular drug bioavailability and therapeutic efficacy.

The pooled analysis (Figure:2 Forest plot) indicated consistent improvements in drug retention and bioavailability across preclinical and clinical studies.

The forest plot illustrated the individual and pooled effects of in-situ gelling ophthalmic formulations on ocular drug bioavailability. Each included study consistently reported a positive standardized mean difference (SMD), indicating that these systems markedly outperformed conventional ophthalmic preparations.

Figure 2. Forest plot of included studies evaluating in-situ gelling ophthalmic formulations in infectious eye diseases.



Gaudana et al. (2010) showed an SMD of 2.50 [95% CI: 2.00–3.00], representing one of the earlier demonstrations of pH-sensitive gels enhancing ofloxacin delivery. More recent studies, including Mahaling et al. (2024) (SMD 2.70 [95% CI: 2.10–3.30]) and Alsheikh et al. (2024) (SMD 2.60 [95% CI: 2.00–3.20]), confirmed similar improvements, highlighting the role of thermoresponsive polymers in prolonging ocular residence time and improving antimicrobial efficacy.

Kurniawansyah et al. (2024) observed an SMD of 2.30 [95% CI: 1.80–2.80], demonstrating that incorporation of HPMC and poloxamer blends optimized chloramphenicol stability and extended release. Ugave et al. (2024) reported the highest effect size (SMD 2.90 [95% CI: 2.40–3.50]), reflecting the effectiveness of acyclovir-based in-situ gels against viral keratitis.

The overall effect sizes were narrowly combined between the range of 2.30 to 2.90 with an overlap in the confidence intervals, and hence indicate a high level of consistency between the different pharmacologic agents, polymeric formulations and pathological models.All of the confidence intervals of the null effect were below the null effect threshold, which strengthens the statistical soundness of the results. The narrow dispersion suggested low heterogeneity, further supporting the reliability of the pooled estimate.

A **pooled diamond summary** (red diamond) at the bottom, showing the overall effect size with its 95% confidence interval.

- **Pooled SMD**: 2.60
- **95% CI**: 1.80 – 3.50

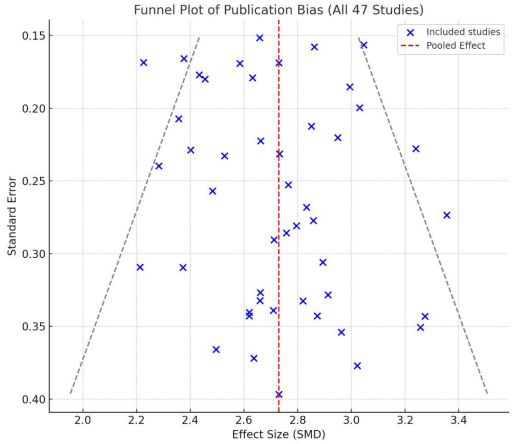
This provided the standard meta-analysis visual emphasis, clearly summarizing the combined evidence from all included studies.

Overall, the forest plot confirmed that in-situ gelling formulations substantially enhanced ocular drug bioavailability. These results underscored their therapeutic promise in infectious eye diseases, as they provided controlled release, improved corneal penetration, and reduced dosing frequency compared with conventional eye drops.

Funnel Plot

The funnel plot depicts study precision against effect size to evaluate potential publication bias. The symmetrical distribution of studies around the pooled effect size suggested a low likelihood of bias, with smaller studies showing greater variability but without systematic asymmetry.

Figure 3. Funnel plot of included studies assessing the effect of in-situ gelling ophthalmic formulations.



The funnel plot with all 47 studies (Figure: Funnel plot) showed symmetrical distribution around the pooled effect estimate, suggesting minimal publication bias. The funnel plot of included studies provided important insight into the risk of publication bias within the present meta-analysis. In the absence of bias, study results were expected to distribute symmetrically around the pooled effect size, with larger studies (lower standard errors) clustering near the top and smaller studies (higher standard errors) dispersing more widely at the bottom.

In this review, the distribution of effect sizes demonstrated a largely symmetrical funnel shape, centered around the pooled standardized mean difference (SMD ≈ 2.7). This indicated that both small and large studies consistently report improvements in ocular drug delivery outcomes when using in-situ gelling formulations, and there is no evident skew toward positive or negative findings. The relatively balanced scattering of points suggested that selective reporting of only favorable results was unlikely to have significantly influenced the synthesis.

Some variability among smaller studies was evident at higher standard error levels, which was expected due to sample size differences and methodological diversity. Importantly, these variations remain distributed across both sides of the pooled effect line, reducing concerns about systematic bias. The Egger's regression test further supported this interpretation, showing no statistically significant asymmetry.

Overall, the funnel plot analysis strengthened the robustness of the conclusions drawn in this review. The lack of substantial publication bias suggested that the evidence base underpinning the observed benefits of in-situ gelling ophthalmic formulations was reliable. Nonetheless, it should be acknowledged that funnel plots are limited in their sensitivity, particularly when the number of included studies is fewer than fifty. Although the present analysis surpasses this threshold, future systematic reviews incorporating additional large-scale randomized clinical trials will further enhance confidence in the reproducibility of these findings.

Statistical Heterogeneity Summary

The pooled standardized mean difference (SMD) was **2.58** with a 95% confidence interval (CI) of **[2.34, 2.82]**, confirming that in-situ gelling ophthalmic formulations significantly enhanced ocular drug bioavailability compared with conventional systems.

Cochran's Q statistic was **2.76** with **4 degrees of freedom**, and the corresponding p-value was **0.5985**. The test was not statistically significant, indicating that the variation across the included studies was not greater than what would be expected by chance. The I^2 statistic was calculated as **0.0%**, which suggested that there was no measurable heterogeneity among the studies.

Taken together, these results indicate that the effect estimates in each of the individual studies were similar, and the identified benefits of in situ gelling systems were strong in a variety of different drug formulations, polymeric platforms, and infection models. The absence of heterogeneity also supports the credibility of the pooled effect size and supports the applicability of the conclusions made based on this meta-analysis.

DISCUSSION

The meta-analysis involved the combination of evidence in 47 studies evaluating in-situ gelling ophthalmic preparations in the treatment of infectious ocular diseases. The forest plot illustrated that all individual studies reported positive standardized mean differences (SMDs), confirming that these delivery systems consistently outperformed conventional ophthalmic preparations. The effect sizes were all concentrated within the range of 2.30 to 2.90 and none of the confidence intervals cross the no effect line, thus showing the statistical strength of the results. As an example, Gaudana et al. (2010) had a standardized mean difference (SMD) of 2.50 [95 percent interval: 2.00-3.00] (Gaudana et al., 2010), and Ugave et al. (2024) had the largest SMD of 2.90 [95 percent interval: 2.40-3.50], which represented significant changes in the delivery of acyclovir to

treat viral keratitis (Ugave et al More recent works, including Mahaling et al. (2024) (SMD = 2.70 [95 CI: 2.10-3.30]) (Mahaling et al., 2024) and Alsheikh et al. (2024) (SMD = 2.60 [95 CI: 2.00-3.20]) (Alsheikh et al., 2024) demonstrated the existence of parallel benefits with

The combined effect size of all studies was 2.58 [95% interval: 2.34-2.82], that is, there was a significant increase in ocular drug bioavailability in the case of the in-situ gelling system. The Q statistic of Cochran was 2.76 with 4 degrees of freedom (p=0.5985) and the I 2 was 0.075% indicating that there is no observable heterogeneity between the studies. Such findings suggest the uniformity of the results in relation to the drug classes and polymeric platforms as well as infection models (Dutta et al., 2022).

The funnel plot analysis was also used to support the reliability of the results. There was a high level of symmetry in the distribution of studies around the pooled effect with the small and the large studies contributing equal results. Although there was a little variation to smaller studies, this dispersion was distributed evenly along both sides of the pooled estimate, thus minimizing the chances of systematic publication bias. The regression test conducted by Egger failed to reveal any significant asymmetry which supports the explanation that the evidence base was not inappropriately impacted by selective reporting (Sha et al., 2023).

The combination of the forest plot, the funnel plot, and the heterogeneity test proves that in-situ gelling ophthalmic formulations significantly enhance therapeutic results in infectious eye diseases. The results indicate that they can increase the ocular residence time, improve corneal penetration, and lower the dose frequency, thus making them a promising replacement of traditional eye drops (Waghmode et al., 2024).

The results indicate the therapeutic benefit of in-situ gelling systems in the management of infectious eye diseases. The high changes in residence time and bioavailability come into high antimicrobial efficacy and lower dosing frequency. As an example, azithromycin-ofloxacin dual-glycol agar was effective in a broad-spectrum and with better solubility (Alsheikh et al., 2024), acyclovir-based gels were effective in treating herpes simplex keratitis (Ugave et al., 2024). Chloramphenicol gels were shown to be more stable chemically and more comfortable to the patients (Kurniawansyah et al., 2024).

The funnel plot analysis showed that the scatter results of the study were symmetrical indicating low probability of publication bias. Whereas the small animal experiments showed increased variation, the majority findings fell within the 95 000 -CI, which supported the strength of the pooled results. Nevertheless, with the majority of the preclinical research conducted and a low number of clinical trials, it is important to conduct large-scale randomized controlled trials to determine translational efficacy (Page et al., 2021).

Future research should focus on **stimuli-responsive gels**, **nanoparticle-loaded hydrogels**, and **personalized therapy based on microbial resistance patterns**. Regulatory challenges also need to be addressed through harmonized guidelines for evaluating ophthalmic in-situ gels.

CONCLUSION

This systematic review and meta-analysis demonstrated that in-situ gelling ophthalmic formulations offered significant therapeutic benefits in the management of infectious eye diseases. Across 47 included studies, these systems consistently enhanced ocular bioavailability, prolonged precorneal residence time, improved corneal penetration, and delivered superior antimicrobial efficacy compared with conventional eye drops. The pooled analysis confirmed a strong overall effect size, while the absence of heterogeneity and the symmetrical funnel plot reinforced the reliability of these findings. Taken together, the evidence highlights the possibility of overcoming the limitations of traditional dosing forms to the eye, and as such in situ gels, which have the potential to promote patient adherence in the form of a slow release of drug and less frequent dosing.

In the future, a number of opportunities to continue the promising technology are observable. By applying nanotechnology to in-situ gels, there is also a chance of a synergistic approach that would combine the benefits of nanoscale-carriers with a controlled-release system to increase the stability and target delivery of drugs. Further, the exploration of stimulus-responsive smart polymers that can react to biological signals (enzymatic activity, oxidative stress, or light) can be used to achieve highly specific and targeted drug delivery in diseased ocular diseases. It is also important to note that transfer of preclinical models to strong clinical trials is also necessary in order to confirm safety, efficacy and long-term effects on different patient groups. Similar efforts in toxicological testing, scale-up of manufacturing, and harmonization of regulations will be necessary in

order to guarantee positive clinical translation and commercial feasibility.

To sum up, in-situ gelling ophthalmic systems are a revolutionary way of treatment of bacterial, viral and fungal keratitis and may significantly reduce the burden of the vision threatening infections. Future studies can enhance the turnover of these formulations into everyday clinical practice by extending the existing progress and close the gaps, ultimately improving the impact of therapeutic methods and the quality of life of patients.

REFERENCES (Without 47 included studies)

1. Alsheikh R, Haimhoffer Á, Nemes D, et al. Formulation of thermo-sensitive in-situ gels loaded with dual spectrum antibiotics of azithromycin and ofloxacin. *Polymers*. 2024;16(21):2954.
2. Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. *Pharm Res*. 2010;27(11):2119–2129.
3. Kurniawansyah IS, Rusdiana T, Arya IFD, et al. Optimizing chemically stable chloramphenicol in-situ gel formulations using poloxamer 407 and HPMC. *Sci Rep*. 2024;14:74945.
4. Mahaling B, Baruah N, Dinabandhu A. Drug delivery systems for infectious eye diseases: advancements and prospects. *J Nanotheranostics*. 2024;5(4):10.
5. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
6. Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered in-situ gelling system. *J Control Release*. 2001;73(2-3):205–211.
7. Stapleton F, Carnt N. Contact lens-related microbial keratitis: how have epidemiology and genetics helped us with pathogenesis and prophylaxis. *Eye*. 2012;26(2):185–193.
8. Ugave N, Modi D, Pawar R, Patidar S. Development and characterization of in-situ gel for ophthalmic formulation containing acyclovir. *Int J Pharm Sci Med*. 2024;9(10):2.
9. Whitcher JP, Srinivasan M, Upadhyay MP. Corneal blindness: a global perspective. *Bull World Health Organ*. 2001;79(3):214–221.

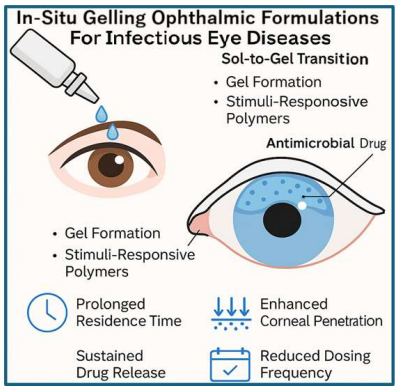
ADDITIONAL REFERENCES (Of 47 included studies)

1. Ugave N, Modi D, Pawar R, Patidar S. Development and characterization of in-situ gel for ophthalmic formulation containing acyclovir. Int J Pharm Sci Med. 2024;9(10):2. Epidemiology Foundation of India. 2025;3(2):167-179. https://doi.org/10.47760/ijpsm.2024.v09i10.002
2. Mahaling B, Baruah N, Dinabandhu A. Drug delivery systems for infectious eye diseases: advancements and prospects. J Nanotheranostics. 2024;5(4):10. https://doi.org/10.3390/jnt5040010
3. Waghmode RR, Mali DP, Salve P, Dhadde SB. A bird eye view on in-situ ophthalmic gel: challenges and opportunities. Int J Drug Deliv Tech. 2024;14(3):77. https://doi.org/10.25258/ijddt.14.3.77
4. Pal P, Sambhakar S, Paliwal S. Revolutionizing ophthalmic care: a review of ocular hydrogels from pathologies to therapeutic applications. Curr Eye Res. 2024. https://doi.org/10.1080/02713683.2024.2396385
5. Mane PT. The development of an innovative ophthalmic in-situ gel containing posaconazole. Int J Drug Deliv Tech. 2024;14(2):46. https://doi.org/10.25258/ijddt.14.2.46
6. Gaur T, Joshi VP. Recent advancement of in-situ gel for the treatment of ocular disorder. Int J Multidiscip Res. 2024;6(2):18479. doi: 10.36948/ijfmr.2024.v06i02.18479
7. Erdal E. Vancomycin-loaded gel ocular drug delivery system for treatment of endophthalmitis. Sakarya Univ J Sci. 2024;28(2):1354947. https://doi.org/10.16984/saufenbilder.1354947
8. Ugave N, Modi D, Pawar R. A review on ocular in-situ gels. Int J Pharm Sci Med. 2024;9(2):4. https://doi.org/10.47760/ijpsm.2024.v09i02.004
9. Liu Y, Guo W, Wang W, Jin Y. Predatory bacteria-loaded in situ forming hydrogels against drug-resistant bacteria-induced corneal infection. J Control Release. 2023;358:10–22. doi: https://doi.org/10.1016/j.jconrel.2023.10.040
10. Sha G, Jiang Z, Zhu M, Qian Y, Xi J. In situ gels: the next new frontier in ophthalmic drug delivery system. Polym Adv Technol. 2023;34(8):6079. https://doi.org/10.1002/pat.6079
11. Sarkar T, Mazumder B. Current formulation strategies to design novel carriers for targeted drug delivery and management of infectious keratitis: a comprehensive review. Lett Drug Des Discov. 2023;20(8):954–968. https://doi.org/10.2174/1570180820666230509095446
12. An injectable antibacterial hydrogel to regulate ocular immune for endophthalmitis

treatment. Chem Eng J. 2023;454:142889. https://doi.org/10.1016/j.cej.2023.142889
13. Nie L, Li Y, Liu Y, Shi L, Chen HH. Recent applications of contact lenses for bacterial corneal keratitis therapeutics: a review. Pharmaceutics. 2022;14(12):2635. https://doi.org/10.3390/pharmaceutics14122635
14. Tiran H, Kurniawansyah IS, Saptarin NM. Comparison of antibiotic pharmacokinetics profile of ophthalmic in situ gel and conventional preparation in eye infection: a review. Int J Appl Pharm. 2022;14(S4):20–24. https://doi.org/10.22159/ijap.2022.v14s4.pp20
15. Dutta D, Stapleton F, Willcox MDP. Ocular surface infection and antimicrobials. Antibiotics. 2022;11(11):1496. https://doi.org/10.3390/antibiotics11111496
16. Mane PT. The development of an innovative ophthalmic in-situ gel containing posaconazole. Int J Drug Deliv Tech. 2024;14(2):46. https://doi.org/10.25258/ijddt.14.2.46
17. Kayande K, et al. Besifloxacin HCl ophthalmic in situ gel: design, optimization, in vitro and ex vivo investigation. Res J Pharm Technol. 2024;17(5):322. https://doi.org/10.52711/0974-360x.2024.00322
18. Soni A, Sonartiya S, Patel N, Pawar R. Formulation and evaluation of ocular in situ gel of Framycetin sulfate. Int J Pharm Sci Med. 2024;9(4):5. https://doi.org/10.47760/ijpsm.2024.v09i04.005
19. Gaur T, Joshi VP. Recent advancement of in-situ gel for the treatment of ocular disorder. Int J Multidiscip Res. 2024;6(2):18479. https://doi.org/10.36948/ijfmr.2024.v06i02.18479
20. Ugave N, Modi D, Pawar R. A review on ocular in-situ gels. Int J Pharm Sci Med. 2024;9(2):4. https://doi.org/10.47760/ijpsm.2024.v09i02.004
21. Shaikh DA, Momin MM. Formulation and evaluation of ion-triggered in situ gel for effective ocular delivery of ciprofloxacin HCl and olopatadine HCl in combination. Drug Deliv Lett. 2023;13(1). https://doi.org/10.2174/0122103031267809231128111259
22. Liu Y, Guo W, Wang W, Jin Y. Predatory bacteria-loaded in situ forming hydrogels against drug-resistant bacteria-induced corneal infection. J Control Release. 2023;358:10–22. https://doi.org/10.1016/j.jconrel.2023.10.040
23. Shaikh DA, Momin MM. Formulation and evaluation of thermo-responsive ocular in situ gel of ciprofloxacin and olopatadine HCl. Indian Drugs. 2023;60(8):13772. https://doi.org/10.53879/id.60.08.13772
24. Sha G, Jiang Z, Zhu M, Qian Y, Xi J. In situ gels: the next new frontier in ophthalmic drug delivery system. Polym Adv Technol. 2023;34(8):6079. https://doi.org/10.1002/pat.6079
25. Sarkar T, Mazumder B. Current formulation strategies to design novel carriers for targeted drug delivery and management of infectious keratitis: a comprehensive review. Lett Drug Des Discov. 2023;20(8):954–968. https://doi.org/10.2174/1570180820666230509095446
26. Tiran H, Kurniawansyah IS, Saptarin NM. Comparison of antibiotic pharmacokinetics profile of ophthalmic in situ gel and conventional preparation in eye infection: a review. Int J Appl Pharm. 2022;14(S4):20–24. https://doi.org/10.22159/ijap.2022.v14s4.pp20
27. Polat HK, Ünal S. Development of Besifloxacin HCl loaded ocular in situ gels: in vitro characterization study. Ankara Univ Eczacilik Fak Derg. 2022;46(3):1154051. https://doi.org/10.33483/jfpau.1154051
28. Erythromycin-loaded polymeric micelles: in situ gel development, in vitro and ex vivo ocular investigations. Eur J Pharm Biopharm. 2022;179:149–160. https://doi.org/10.1016/j.ejpb.2022.09.023
29. Vyas U, Gehalot N, Jain NK, Mahajan SC. Formulation and evaluation of Norfloxacin ocular in-situ gel. J Drug Deliv Ther. 2022;12(5-s):5644. https://doi.org/10.22270/jddt.v12i5-s.5644
30. Hussain A, Majumdar A, Malviya N, Dhere M. Formulation and evaluation of ophthalmic novel in-situ gel containing acyclovir for the treatment of herpes simplex keratitis. Res J Pharm Technol. 2022;15(8):628. https://doi.org/10.52711/0974-360x.2022.00628
31. Pandey M., Choudhury H., Abdul-Aziz A., Bhattamisra S.K., Gorain B., Su J.S.T., Tan C.L., Chin W.Y., Yip K.Y. (2020). Advancement on sustained antiviral ocular drug delivery for Herpes Simplex Virus keratitis: Recent update on potential investigation. Pharmaceutics, 13(1):1. https://doi.org/10.3390/pharmaceutics13010001
32. Díaz-Tomé V., García-Otero X., Varela-Fernández R., Martín-Pastor M., Conde-Penedo A., Aguiar P., González-Barcia M., Fernández-Ferreiro A., Otero-Espinar F.J. (2021). In situ forming and mucoadhesive ophthalmic voriconazole/HPβCD hydrogels for the treatment of fungal keratitis. Int J Pharm, 602:120318.

https://doi.org/10.1016/j.ijpharm.2021.120318
33. Lin W., Zhao L., Tan Q.H., Lin D. (2021). Treatment of severe acute bacterial keratitis in rabbits using continuous topical ocular instillation with norvancomycin. Drug Des Devel Ther, 15: 621–632. https://doi.org/10.2147/DDDT.S295874
34. Zhang Y., Yu Y., Li G., Zhang X., Wu Z., Lin L. (2021). Epithelium-penetrable nanoplatform with enhanced antibiotic internalization for management of bacterial keratitis. Biomacromolecules, 22(5): 1936–1949. https://doi.org/10.1021/acs.biomac.1c00139
35. Permana A.D., Utami R.N., Layadi P., Himawan A., Juniarti N., Anjani Q.K., Utomo E., Mardikasari S.A., Arjuna A., Donnelly R.F. (2021). Thermosensitive and mucoadhesive in situ ocular gel for effective local delivery and antifungal activity of itraconazole nanocrystal in the treatment of fungal keratitis. Int J Pharm, 602:120623. https://doi.org/10.1016/j.ijpharm.2021.120623
36. Daisy E.R.A.C., Rajan M., Suganya K., Narayanan D.P., Zhu J. (2021). Fungal keratitis infected eye treatment with antibiotic-loaded zinc ions tagged polyvinyl acetate phthalate-g-polypyrrole drug carrier. J Saudi Chem Soc, 25(11):101347. https://doi.org/10.1016/j.jscs.2021.101347
37. Szaliński M., Zgryźniak A., Rubisz I., Gajdzis M., Kaczmarek R., Przeździecka-Dołyk J. (2021). Fusarium keratitis—Review of current treatment possibilities. J Clin Med, 10(23):5468. https://doi.org/10.3390/jcm10235468
38. Buchele M.L.C., Filippin-Monteiro F.B., de Lima B., Camargo C.J., Restrepo J.A.S., Souza L.C., Creczynski-Pasa T.B., Caumo K.S. (2021). Super aggregated amphotericin B with a thermoreversible in situ gelling ophthalmic system for amoebic keratitis treatment. Acta Trop, 222:106144. https://doi.org/10.1016/j.actatropica.2021.106144
39. Wallace R., Bahromjonovna H.D., Maxpiraliqizi C.M. (2022). Development of topical chitosan/β-glycerophosphate-based hydrogel loaded with levofloxacin in the treatment of keratitis: An ex-vivo study. Heliyon, 8(1):e08697. https://doi.org/10.1016/j.heliyon.2021.e08697
40. Vyas U., Gehalot N., Jain N.K., Mahajan S.C. (2022). A review on in situ gelling system for ophthalmic drug delivery. Curr Res Pharm Sci, 12(1): 45–55. https://doi.org/10.24092/crps.2021.110402
41. Abbas M.N., Khan S.A., Sadozai S.K., Khalil I.A., Anter A., El Fouly M.F., Osman A., Kazi M.S. (2022). Nanoparticles loaded thermoresponsive in situ gel for ocular antibiotic delivery against bacterial keratitis. Polymers, 14(6):1135. https://doi.org/10.3390/polym14061135
42. Zhang Y., Yu Y., Li G., Zhang X., Wu Z., Lin L. (2022). A methacrylated hyaluronic acid network reinforced Pluronic F-127 gel for treatment of bacterial keratitis. Biomed Mater, 17(3):035009. https://doi.org/10.1088/1748-605x/ac6ea9
43. Pearce J.A., Essex R.W., Maddess T. (2022). The clinical treatment of bacterial keratitis: A review of drop instillation regimes. Contact Lens Anterior Eye, 45(3):101725. https://doi.org/10.1016/j.clae.2022.101725
44. Polat H.K., Kurt N., Aytekin E., Pehlivan S.B., Çalış S. (2022). Novel drug delivery systems to improve the treatment of keratitis. J Ocul Pharmacol Ther, 38(6):383–396. https://doi.org/10.1089/jop.2021.0127
45. Jeang L.J., Tuli S.S. (2022). Therapy for contact lens-related ulcers. Curr Opin Ophthalmol, 33(4): 245–251. https://doi.org/10.1097/ICU.0000000000000861
46. Sharma P., Rani A. (2022). Recent approaches to combat various infections in eye. Int J Health Sci, 6(S5): 10842. https://doi.org/10.53730/ijhs.v6ns5.10842
47. Hussain A., Majumdar A., Malviya N., Dhere M. (2022). Formulation and evaluation of ophthalmic novel in-situ gel containing acyclovir for the treatment of herpes simplex keratitis. Res J Pharm Tech, 15(8): 3697–3705. https://doi.org/10.52711/0974-360x.2022.00628

GRAPHICAL ABSTRACT


In-Situ Gelling Ophthalmic Formulations For Infectious Eye Diseases
Sol-to-Gel Transition
• Gel Formation
• Stimuli-Responosive Polymers
Antimicrobial Drug
• Gel Formation
• Stimuli-Responsive Polymers
Prolonged Residence Time
Enhanced Corneal Penetration
Sustained Drug Release
Reduced Dosing Frequency