A Review: Formulation and Evaluation of Norfloxacin in Situ Ophthalmic Gel

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***Abstract*—Conventional ophthalmic solutions suffer from rapid pre-corneal elimination, resulting in poor bioavailability and suboptimal therapeutic efficacy. In situ gel-forming systems represent a promising alternative, transitioning from a liquid to a gel phase upon instillation into the conjunctival cul-de-sac in response to physiological stimuli such as pH, temperature, or ionic strength. This review describes the formulation and evaluation of an ophthalmic in situ gelling system loaded with Norfloxacin, a broad-spectrum fluoroquinolone antibacterial agent, intended for the treatment of bacterial conjunctivitis, corneal ulcers, and blepharitis. Carbopol 940 was employed as the pH-sensitive gelling agent in combination with HPMC K15M as a viscosity enhancer. Five formulations (F1–F5) were prepared and evaluated for physicochemical parameters including clarity, pH, gelling capacity, viscosity, drug content, in vitro drug diffusion, antibacterial activity, and accelerated stability. Formulation F5 demonstrated optimal performance, achieving 81.43% drug release over 8 hours with a sustained release profile. FTIR and DSC analyses confirmed absence of drug–excipient interactions. Stability studies under ICH guidelines confirmed robustness of the optimized formulation. The developed system offers enhanced ocular retention and controlled drug release compared to conventional eye drops.**

***Index Terms*—In situ gel, Norfloxacin, Carbopol 940, HPMC K15M, Ocular drug delivery, pH-triggered gelation, Antibacterial.**

I. INTRODUCTION

The eye is a unique and complex organ with specialized anatomy that makes targeted drug delivery both feasible and challenging. Ocular drug delivery is primarily carried out via the topical route due to its convenience, needle-free nature, and ability to achieve localized therapeutic concentrations while avoiding systemic side effects [1]. However, conventional ophthalmic solutions are severely limited by pre-corneal loss mechanisms: the conjunctival cul-de-sac holds only approximately 7 µL, whereas a standard eye dropper delivers 50–75 µL per drop. The excess volume drains rapidly through the nasolacrimal duct, reducing corneal contact time to 1–2 minutes and limiting bioavailability to less than 5–10% of the instilled dose [2].

The barriers to effective ocular drug delivery include tear dilution, nasolacrimal drainage, systemic absorption via nasal mucosa, conjunctival absorption, and enzymatic metabolism in the pre-corneal space. Additionally, the corneal epithelium constitutes a significant lipophilic barrier to hydrophilic drugs [3]. Physiological protective mechanisms such as blinking (15–20 times/minute), lacrimation, and normal tear turnover (approximately 16% per minute) further compromise drug retention.

To overcome these limitations, researchers have focused on novel drug delivery strategies that prolong the residence time of drugs on the ocular surface and control their release. In situ gel-forming systems represent one of the most promising approaches. These systems are installed as aqueous solutions, which undergo a sol-to-gel phase transition upon contact with the tear fluid due to changes in temperature, pH, or ionic strength [4]. The resulting gel increases pre-corneal residence time, reduces dosing frequency, and improves patient compliance compared to conventional eye drops and preformed gels.

II. RATIONALE FOR IN SITU GEL SYSTEMS

Traditional ophthalmic formulations including eye drops, ointments, and suspensions have several drawbacks. Eye drops, despite being the most widely used, offer less than 1% absorption of the instilled dose due to rapid elimination [5]. Ointments provide

extended contact time but cause blurred vision and patient discomfort, limiting compliance. Preformed gels are difficult to administer as drops and result in variable dosing. Ocular inserts offer prolonged drug release but require professional placement and may cause irritation.

In situ gelling systems address these shortcomings by: (i) being easily instilled as low-viscosity solutions; (ii) undergoing rapid gelation at the ocular surface; (iii) providing sustained, controlled drug release; (iv) reducing nasolacrimal drainage and systemic side effects; and (v) improving patient comfort and compliance compared to preformed gels [6]. These characteristics make in situ ophthalmic gels a highly relevant platform for the sustained delivery of antibacterial agents like Norfloxacin.

III. DRUG AND EXCIPIENT PROFILE

A. Norfloxacin

Norfloxacin is a second-generation fluoroquinolone antibiotic with a molecular formula of $C_{16}H_{18}FN_3O_3$ and a molecular weight of 319.33 g/mol. Its IUPAC name is 1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid. It is a synthetic broad-spectrum antibacterial agent effective against most Gram-positive and Gram-negative organisms. Its bactericidal mechanism involves inhibition of bacterial DNA gyrase (topoisomerase II) and topoisomerase IV, enzymes essential for DNA replication, transcription, repair, and recombination [7].

Norfloxacin has a melting point of 221°C, aqueous solubility that is very slight at neutral pH, a half-life of 3–4 hours, protein binding of 10–15%, and oral bioavailability of 80–90%. The fluorine atom at position 6 enhances potency against Gram-negative organisms, while the piperazine moiety at position 7 confers anti-pseudomonal activity. In ophthalmic practice, it is used at a 0.3% w/v concentration for bacterial conjunctivitis, blepharitis, and corneal ulcers.

B. Carbopol 940

Carbopol 940 is a lightly cross-linked polyacrylic acid polymer (molecular formula $C_3H_4O_2$; MW: 72.06 g/mol) that serves as a pH-sensitive gelling agent. At acidic pH (2.5–3.0), it exists as a free-flowing white powder. Upon neutralization to physiological pH (7.4), the polymer undergoes ionization, resulting in dramatic viscosity increase and gel formation via electrostatic repulsion and hydrogen bonding [8]. It is considered nontoxic, nonirritant, and biocompatible for ophthalmic use.

C. HPMC K15M

Hydroxypropyl methylcellulose (HPMC K15M) is a water-soluble semisynthetic cellulose ether with a molecular weight of 1261.45 g/mol. It functions as a viscosity-enhancing polymer and mucoadhesive agent. It is odorless, tasteless, white fibrous powder soluble in cold water, nonionic, and compatible with most ionic excipients. In ophthalmic formulations, HPMC prolongs precorneal drug residence time and modulates drug release kinetics. Its incorporation alongside Carbopol 940 allows reduction in the concentration of primary gelling agent while optimizing gel strength [9].

D. Other Excipients

Mannitol (MW: 182.17 g/mol) was employed as an isotonicity-adjusting agent, ensuring the formulation's osmolality matches that of tear fluid (approximately 300 mOsm/kg). Benzalkonium chloride (BKC; 0.01% w/v) was used as an antimicrobial preservative, a quaternary ammonium compound widely accepted in ophthalmic preparations [10]. Acetate buffer (pH 5.0) was prepared as the vehicle to maintain the acidic pre-gelation pH of the formulation.

IV. IN SITU GELATION MECHANISMS

Three principal mechanisms are exploited in in situ ophthalmic gel design:

1. pH-Triggered Gelation: Carbopol 940 and cellulose acetate phthalate (CAP) are formulated at pH 4–5 and undergo sol-to-gel transition at physiological tear pH of 7.4, due to ionization of carboxylic groups leading to polymer chain extension and viscosity increase [11].
2. Temperature-Sensitive Gelation: Poloxamer 407 (Pluronic F-127) remains liquid at room temperature (below 25°C) and gels at ocular surface temperature (~34°C) due to micelle aggregation above the critical micelle concentration [12].
3. Ion-Activated Gelation: Gellan gum (Gelrite), sodium alginate, and xanthan gum form gels upon contact with cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) in tear fluid through ionic crosslinking [13].

The present formulation employed a pH-triggered mechanism using Carbopol 940 as the primary gelling agent, exploiting the pH difference between the acidic formulation (pH ~5.0) and tear fluid (pH 7.4).

V. MATERIALS AND METHODS

A. Materials

Norfloxacin was obtained from Labware Chemicals, Mumbai; Carbopol 940 from Maher Chemicals, Mumbai; HPMC K15M from Kemphasol, Mumbai; mannitol from Thomas Baker Pvt. Ltd., Mumbai; and benzalkonium chloride from Moly Chem Ltd., Mumbai. All chemicals were of pharmaceutical/analytical grade.

B. Preformulation Studies

Preformulation evaluation of the drug included assessment of organoleptic properties (colour, odour, taste, nature), melting point determination by digital melting point apparatus, and solubility profile in various solvents. UV spectroscopy was performed using a Shimadzu UV-1800 spectrophotometer to determine the wavelength of maximum absorption (λmax) of Norfloxacin in simulated tear fluid (STF, pH 7.4). The drug exhibited characteristic absorption at 272 nm, and a standard calibration curve was established over the concentration range of 2–10 µg/mL with correlation coefficient $R^2 = 0.9985$.

Drug–excipient compatibility was studied by FTIR (PerkinElmer, 400–4000 cm^{-1}) and DSC (Shimadzu DSC-60, heated from 50°C to 300°C at 20°C/min). FTIR confirmed key functional groups of Norfloxacin (O-H stretch: 3438.86 cm^{-1}; C-H stretch: 2925.13 cm^{-1}; C=C stretch: 1614.22 cm^{-1}; C-O stretch: 1211.89 cm^{-1}). DSC showed a characteristic endothermic peak at 221.30°C with no significant new peaks in excipient mixtures, confirming absence of chemical interaction [14].

C. Formulation of In Situ Gel

Five formulations (F1–F5) were prepared by varying concentrations of Carbopol 940 (0.08–0.24% w/v) and HPMC K15M (0.08–0.24% w/v) while keeping Norfloxacin (0.3% w/v), mannitol (2.0 g), benzalkonium chloride (0.004 ml), and acetate buffer (4 ml) constant. HPMC K15M was slowly hydrated in acetate buffer under magnetic stirring. Norfloxacin was dissolved and added to the polymer solution. Carbopol 940 was dispersed separately and incorporated. pH was adjusted to 5.0 ± 0.2. The formulation was filled into amber vials and sterilized by autoclave at 121°C/15 psi for 20 minutes [15].

VI. EVALUATION PARAMETERS

A. Clarity: All formulations were visually inspected for clarity against black and white backgrounds under a good light source. All five formulations (F1–F5) appeared clear and free from visible particulates.

B. pH: pH was measured using an Elico India Systronics digital pH meter. The pH of formulations F1–F5 ranged from 5.9 to 6.9, well within acceptable ophthalmic limits (5.0–7.4), with F5 recording pH 6.9 [16].

C. Gelling Capacity: Gelling capacity was evaluated by placing one drop of formulation into 2 mL of freshly prepared artificial tear fluid (pH 7.4) at 37°C. All formulations gelled instantaneously. Values ranged from 0.057 (F1) to 0.178 (F5), indicating F5 produced the most robust gel.

D. Viscosity: Viscosity was determined using a Brookfield DV-III+ Rheometer (spindle No. 4, 1–60 rpm). All formulations exhibited pseudoplastic (shear-thinning) rheological behaviour. Viscosity ranged from 991 cP (F1) to 1456 cP (F5) [17].

E. Drug Content: Drug content was determined by UV-Vis spectrophotometry at 272 nm. All formulations showed drug content between 79.56% and 85.23%, with F5 recording the highest content of 85.23%, confirming uniform drug distribution throughout the gel matrix.

F. In Vitro Drug Diffusion: Drug diffusion was evaluated using cellophane membrane diffusion cells in simulated tear fluid (pH 7.4) at 37 ± 1°C. Formulation F5 demonstrated the highest cumulative drug release of 81.43% at 8 hours, following Korsmeyer–Peppas kinetics, indicating diffusion-controlled release [18].

G. Antibacterial Activity: Antibacterial efficacy was assessed by agar well diffusion using Staphylococcus aureus and Pseudomonas aeruginosa. Formulation F5

produced zones of inhibition of 43 mm against S. aureus and 40 mm against P. aeruginosa, comparable to pure Norfloxacin (48 mm and 44 mm, respectively) [19].

H. Spreadability: Spreadability ranged from 5.62 g·cm/sec (F1) to 7.58 g·cm/sec (F5), confirming that F5 can be evenly distributed over the ocular surface for uniform drug availability.

I. Stability Studies: Accelerated stability testing (ICH Q1A; 40 ± 2°C, 75 ± 5% RH, 3 months) showed no significant changes in physical appearance, pH, spreadability, viscosity, or drug release, confirming the stability of the optimized formulation.

VII. RESULTS AND DISCUSSION

Preformulation studies confirmed the identity and purity of Norfloxacin. The melting point was 221°C, consistent with the pharmacopoeial standard. FTIR spectra of drug–excipient mixtures retained all characteristic peaks of pure drug without new peaks or significant shifts, establishing compatibility of Norfloxacin with Carbopol 940 and HPMC K15M. DSC thermograms showed minimal change in the characteristic endothermic peak, indicating no polymorphic transformation or degradation.

Among all five formulations, F5 (Carbopol 940: 0.08% w/v; HPMC K15M: 0.24% w/v) emerged as optimal based on the totality of evaluation parameters: pH 6.9, highest gelling capacity (0.178), highest viscosity (1456 cP), drug content 85.23%, and sustained release of 81.43% at 8 hours. The synergistic combination of Carbopol 940 and HPMC K15M produced a gel matrix that effectively sustained drug release while maintaining acceptable clarity and patient comfort.

The antibacterial studies confirmed that the gel formulation retained the therapeutic efficacy of Norfloxacin against principal ocular pathogens. The slight reduction in zone of inhibition compared to pure drug is attributed to controlled diffusion from the gel network, consistent with the desired sustained-release objective. Stability data demonstrated no significant change in physicochemical properties under accelerated conditions, establishing robustness and shelf-life of the optimized formulation.

VIII. CONCLUSION

A pH-triggered in situ ophthalmic gel of Norfloxacin was successfully formulated and evaluated using Carbopol 940 as the gelling agent and HPMC K15M as the viscosity enhancer. The system transitions from a liquid to a gel upon contact with tear fluid, extending pre-corneal residence time and enabling sustained drug release. Among the five formulations, F5 demonstrated optimal physicochemical properties: pH 6.9, gelling capacity 0.178, viscosity 1456 cP, drug content 85.23%, and 81.43% cumulative release at 8 hours. The formulation exhibited significant antibacterial activity against S. aureus and P. aeruginosa and was stable under ICH accelerated conditions.

The in-situ gel approach addresses the fundamental limitations of conventional ophthalmic drops by reducing dosing frequency, minimizing nasolacrimal drainage, and enhancing ocular bioavailability. The methodology is industrially scalable and economically viable, representing a promising alternative to conventional ophthalmic delivery systems for Norfloxacin and analogous antibacterial agents.

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