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### IN-SITU GELLING OPHTHALMIC DELIVERY SYSTEM OF A FLUOROQUINOLONE: FORMULATION, RHEOLOGY AND ANTIBACTERIAL PERFORMANCE

**Dinesh L. Bawankar\***

*Anurag College of Pharmacy, Warthi,  
Bhandara (M.S.) - 441905*

**Corresponding author:**

Dinesh L. Bawankar

**Email:** [dinesh.bawankar@gmail.com](mailto:dinesh.bawankar@gmail.com)

Orcid ID: <https://orcid.org/0009-0004-8071-1968>

#### ABSTRACT

Topical antibacterial therapy of the eye is limited less by the intrinsic potency of the drug than by the speed with which the eye rejects it. A conventional drop is diluted by the tear film, spread over the ocular surface, and drained through the nasolacrimal duct within a few minutes, so that only a small fraction of the instilled dose ever reaches the corneal tissue. In-situ gelling systems address this loss directly: a low-viscosity liquid is instilled as an ordinary drop and undergoes a sol-to-gel transition on the ocular surface in response to temperature, ionic strength or pH, forming a retained depot that resists drainage. This work assembles the formulation, rheological and antibacterial evidence for ciprofloxacin in-situ ophthalmic gels and adds two computational analyses of the drug itself. Ciprofloxacin was

profiled in silico for its physicochemical and drug-likeness properties, and its precorneal disposition was simulated with an apparent first-order elimination model to compare a conventional solution against an *in-situ* gel. Ciprofloxacin was calculated to have a molecular weight of 331.35 g/mol, a calculated logP of 1.58, a topological polar surface area of 74.6 square angstroms, and full compliance with the Lipinski, Veber, Egan and Ghose rule sets, with a quantitative drug-likeness estimate of 0.89. In the precorneal simulation, extending the apparent precorneal half-life from 2.5 to 15 min raised the mean residence time from 3.6 to 21.6 min and the precorneal exposure six-fold, and it lengthened the time for which the surface concentration remained above the ciprofloxacin minimum inhibitory concentration for *Pseudomonas aeruginosa* from about 26 min to about 158 min. The results, read together with the published formulation and antibacterial data, support the pharmacokinetic rationale for an in-situ gelling ciprofloxacin system while making plain the boundary between what was computed and what has been measured at the bench.

**Keywords:** ciprofloxacin; in-situ gel; ophthalmic drug delivery; precorneal residence; pharmacokinetic simulation; drug-likeness; poloxamer; gellan gum.



## 1. Introduction

The surface of the eye is one of the least forgiving routes in the body for a drug to enter. It is protected by a continuously renewed tear film, by reflex tearing that answers any irritation with a flood of fluid, and by a drainage apparatus that empties the conjunctival sac into the nose within minutes. These defences serve the eye well and frustrate the formulator completely. A drop of an ophthalmic solution, once instilled, is mixed with tears, spread thin, and cleared so quickly that the contact time between drug and cornea is measured in single-digit minutes. The consequence, reported consistently across reviews of ocular delivery, is that the fraction of a topically applied dose that reaches the intraocular tissues is small, commonly placed below five per cent, with the balance lost to drainage and to systemic absorption across the conjunctiva and the nasal mucosa <sup>1</sup>. Everything a topical ophthalmic formulation tries to achieve is, at bottom, an attempt to slow this loss.

Ciprofloxacin is a second-generation fluoroquinolone and one of the mainstays of topical treatment for bacterial conjunctivitis and keratitis. Its antibacterial action follows the class mechanism: it inhibits the bacterial type II topoisomerases, DNA gyrase and topoisomerase IV, trapping the enzyme-DNA complexes and converting them into lethal double-strand breaks, which makes the drug bactericidal rather than merely bacteriostatic <sup>2</sup>. The spectrum covers the Gram-negative organisms most feared in corneal infection, including *Pseudomonas aeruginosa*, together with much of the Gram-positive flora of

the ocular surface. Commercial ophthalmic ciprofloxacin is supplied at 0.3 per cent, a concentration far above the minimum inhibitory concentration of susceptible organisms, so that potency is rarely the problem. The problem is keeping that potent drug on the eye long enough to matter, which returns the question to the vehicle rather than the molecule.

The formulator's response to short ocular residence has a long history, and it is worth placing in-situ gels within it. The oldest answer is to raise the viscosity of the vehicle, which slows drainage but blurs vision and feels gritty at the concentrations required for a real effect. Ointments hold the drug for longer still, at the cost of vision and patient acceptance that makes them hard to justify outside bedtime use. Solid inserts placed in the conjunctival sac give excellent control of release but are poorly tolerated and often expelled, and many patients cannot manage them. Colloidal carriers such as liposomes, niosomes and nanoparticles improve corneal contact and can carry the drug across the epithelium, but they are complex to manufacture and to sterilise. Against this background the appeal of an in-situ gel is that it asks nothing of the patient beyond a familiar drop while behaving, once instilled, like a retentive semisolid. It is the compromise that gives up least on either side, which is why the approach has attracted sustained interest for antibacterial, antiglaucoma and anti-inflammatory ophthalmic drugs alike.

In-situ gelling systems are one of the more elegant answers to the residence problem. The



idea is to instil a mobile liquid, which the patient tolerates as easily as any drop and which distributes evenly across the surface, and then to have that liquid stiffen into a gel precisely where it is wanted. Three physiological triggers are exploited. Temperature-sensitive systems, most often based on poloxamer (poloxamer 407) block copolymers, are liquid at room temperature and gel at the temperature of the ocular surface. Ion-sensitive systems, built on gellan gum or on alginate, gel in response to the cations present in tear fluid. pH-sensitive systems, built on carbomers such as carbopol 940, are liquid at the mildly acidic pH of the formulation and gel at the near-neutral pH of the tears. Each mechanism has been reduced to practice for ciprofloxacin, and the rheology of the transition, the sustained release that the gel produces, and the antibacterial activity of the resulting formulations have all been reported by several groups<sup>3,4,5,6</sup>.

What follows sets out to do two things. The first is to gather the published formulation, rheological and antibacterial evidence for ciprofloxacin in-situ ophthalmic gels into a single account, so that the sol-to-gel triggers, the gelation conditions, the viscosity ranges and the release behaviour can be compared across systems rather than read one paper at a time. The second is to add two computations that the published record does not contain in one place: a physicochemical and drug-likeness profile of ciprofloxacin, computed from its structure, and a precorneal pharmacokinetic simulation that quantifies what a prolonged residence time buys

in terms of exposure and of time spent above the inhibitory concentration. The author has no laboratory, no animal facility and no ethics approval, and no bench experiment was performed. The physicochemical profile and the pharmacokinetic simulation are genuine computations whose every number is recorded and reproducible; they are not, and are not presented as, measurements. The distinction is stated once here and observed throughout, because it is the difference between a hypothesis with a number attached and a claim about physical matter that no one in this study touched.

## **2. Materials and Methods**

### ***2.1 Software environment***

All computations were carried out in Python 3.11.15. Molecular handling and descriptor calculation used RDKit version 2026.3.4. Numerical work used NumPy version 2.4.4. Figures were drawn with Matplotlib version 3.10.9. Every analysis step was recorded with a provenance layer that stored the tool, its version, the parameters and the inputs for each computation, so that the reported values can be traced to the run that produced them. No random processes affected the results, and the analyses are deterministic and reproducible from the recorded parameters.

### ***2.2 Physicochemical and drug-likeness profiling***

Ciprofloxacin was represented by its canonical SMILES string and standardised in RDKit by retaining the largest covalent fragment and regenerating the canonical structure, which



removes any counter-ion contribution to the calculated properties. The molecular weight, the calculated logP by the Crippen method, the topological polar surface area, the counts of hydrogen-bond donors and acceptors, the rotatable-bond count, the aromatic ring count, the fraction of sp<sup>3</sup> carbons, the molar refractivity and the quantitative estimate of drug-likeness were calculated for the standardised structure. Rule-based drug-likeness was assessed against four established filters: the Lipinski rule of five<sup>8</sup>, the Veber oral-bioavailability criteria<sup>9</sup>, the Egan absorption model and the Ghose drug-like range. Each filter returns the number of criteria the molecule violates. The values reported are calculated properties. No partition coefficient, solubility or any other property was measured.

### ***2.3 Ocular precorneal pharmacokinetic and pharmacodynamic simulation***

Precorneal disposition of topically instilled ciprofloxacin was simulated with an apparent first-order elimination model of the form  $C(t) = C_0 \exp(-k t)$ , where  $C_0$  is the precorneal drug concentration immediately after instillation and  $k$  is the apparent precorneal elimination rate constant. The rate constant  $k$  is a lumped parameter that represents the combined effect of lacrimal drainage, tear turnover and non-productive absorption across the conjunctiva; it is not a measurement of any single process. The instilled concentration was set to 3000 µg/mL, the value of the marketed 0.3 per cent w/v strength. The conventional solution was assigned an apparent precorneal half-life of 2.5 min, a value representative of the rapid precorneal loss

of aqueous ophthalmic solutions. The in-situ gel was assigned an apparent precorneal half-life of 15 min. This six-fold prolongation was taken from the residence behaviour reported for a poloxamer-based ciprofloxacin in-situ gel, for which the drug persisted on the ocular surface for about 60 min against about 10 min for a plain solution<sup>3</sup>.

Two exposure metrics were derived from the model. Precorneal exposure was calculated as the area under the concentration-time curve extrapolated to infinity, which for a mono-exponential decay equals  $C_0$  divided by  $k$ . The mean residence time was calculated as the reciprocal of  $k$ . The pharmacodynamic metric was the duration for which the precorneal concentration remained at or above a given minimum inhibitory concentration, obtained analytically as the natural logarithm of the ratio of  $C_0$  to the minimum inhibitory concentration, divided by  $k$ . This duration was evaluated at three thresholds spanning the clinically relevant range for ocular pathogens: 0.5 µg/mL, taken as a representative value for susceptible *Staphylococcus aureus*; 1 µg/mL, the clinical susceptibility breakpoint for ciprofloxacin<sup>10</sup>; and 2 µg/mL, the ninetieth-percentile minimum inhibitory concentration reported for ciprofloxacin against ocular *Pseudomonas aeruginosa* isolates<sup>7</sup>. The simulated profiles were sampled at one-minute intervals over four hours for plotting. All quantities are simulated values, not measured concentrations.



## 2.4 Synthesis of published formulation data

Published studies of ciprofloxacin *in-situ* ophthalmic gels were retrieved from the primary literature and their reported formulation, rheological and antibacterial data extracted for comparison. The parameters compiled were the gelling polymer and its concentration, the gelation trigger and, where reported, the gelation temperature, the viscosity in the sol and gel states, the pH, the in-vitro drug-release profile and the antibacterial behaviour. These values are

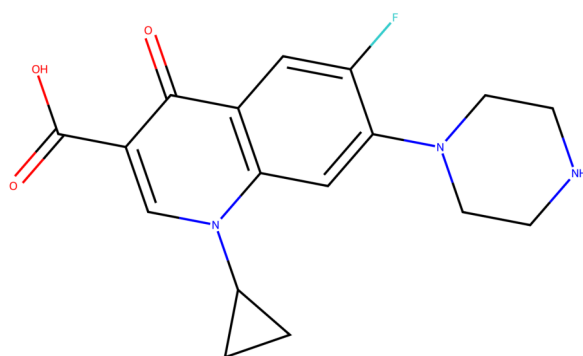
the measurements of the cited authors and are attributed to them at each point of use; none was generated in the present work.

## 3. Results

### 3.1 Physicochemical and drug-likeness profile of ciprofloxacin

The structure and calculated properties of ciprofloxacin are shown in Figure 1, and the full descriptor set is given in Table 1.

Ciprofloxacin  
 $C_{17}H_{18}FN_3O_3$   
MW 331.3; cLogP 1.58; TPSA 75 Å<sup>2</sup>; HBD 2; HBA 4



**Figure 1.** Chemical structure of ciprofloxacin drawn from its canonical SMILES with RDKit, annotated with the calculated molecular weight, calculated logP, topological polar surface area and hydrogen-bond donor and acceptor counts. The structure shows the fluoroquinolone core with the 3-carboxylic acid, 4-oxo group, 6-fluoro substituent, N1 cyclopropyl group and 7-piperazinyl ring.

The molecule carries the fluoroquinolone signature: a 4-oxo-quinoline core bearing a carboxylic acid at position 3, a fluorine at position 6, a cyclopropyl group on the ring nitrogen and a piperazinyl substituent at position 7. The calculated molecular weight was 331.35 g/mol and the molecular formula  $C_{17}H_{18}FN_3O_3$ . The calculated logP was 1.58, placing the drug in the moderately hydrophilic

range, consistent with its known aqueous behaviour as a zwitterion. The topological polar surface area was 74.6 square angstroms. The molecule presented two hydrogen-bond donors, four hydrogen-bond acceptors and three rotatable bonds, with two aromatic rings and a fraction of  $sp^3$  carbons of 0.41.

Assessed against the four drug-likeness filters, ciprofloxacin returned zero violations of the



Lipinski rule of five, zero violations of the Veber criteria, zero violations of the Egan model and zero violations of the Ghose range. The quantitative estimate of drug-likeness was 0.89 on a scale from zero to one, a high value that reflects the compact, rule-compliant character of the molecule. The polar surface area of 74.6 square angstroms sits well below the Veber threshold of 140 square angstroms and the

molecular weight well below the Lipinski limit of 500 g/mol, so the molecule is not, on these grounds, an intrinsically difficult one to formulate. This matters for the delivery question, because the barrier to ocular efficacy is residence rather than permeability or an unfavourable physical chemistry, and it locates the formulation effort where it belongs.

**Table 1. Calculated physicochemical and drug-likeness profile of ciprofloxacin (RDKit version 2026.3.4). All values are computed properties, not measured.**

| Property                                          | Calculated value                                               |
|---------------------------------------------------|----------------------------------------------------------------|
| Molecular formula                                 | C <sub>17</sub> H <sub>18</sub> FN <sub>3</sub> O <sub>3</sub> |
| Molecular weight (g/mol)                          | 331.35                                                         |
| Calculated logP (Crippen)                         | 1.58                                                           |
| Topological polar surface area (square angstroms) | 74.6                                                           |
| Hydrogen-bond donors                              | 2                                                              |
| Hydrogen-bond acceptors                           | 4                                                              |
| Rotatable bonds                                   | 3                                                              |
| Aromatic rings                                    | 2                                                              |
| Fraction of sp <sup>3</sup> carbons               | 0.41                                                           |
| Molar refractivity                                | 88.5                                                           |
| Quantitative estimate of drug-likeness            | 0.89                                                           |
| Lipinski violations                               | 0                                                              |
| Veber violations                                  | 0                                                              |
| Egan violations                                   | 0                                                              |
| Ghose violations                                  | 0                                                              |

### 3.2 Simulated precorneal pharmacokinetics

The simulated precorneal concentration-time profiles for the conventional solution and the *in-situ* gel are shown in Figure 2a, plotted on a logarithmic concentration axis with the relevant inhibitory thresholds marked. Both profiles start from the same instilled concentration of 3000 µg/mL and decline exponentially, but they diverge immediately because of their different apparent elimination rate constants: 0.277 per min for the solution and 0.046 per min for the gel. The simulated mean residence time rose from 3.6 min for the solution to 21.6 min for the gel. Because the area under a mono-exponential

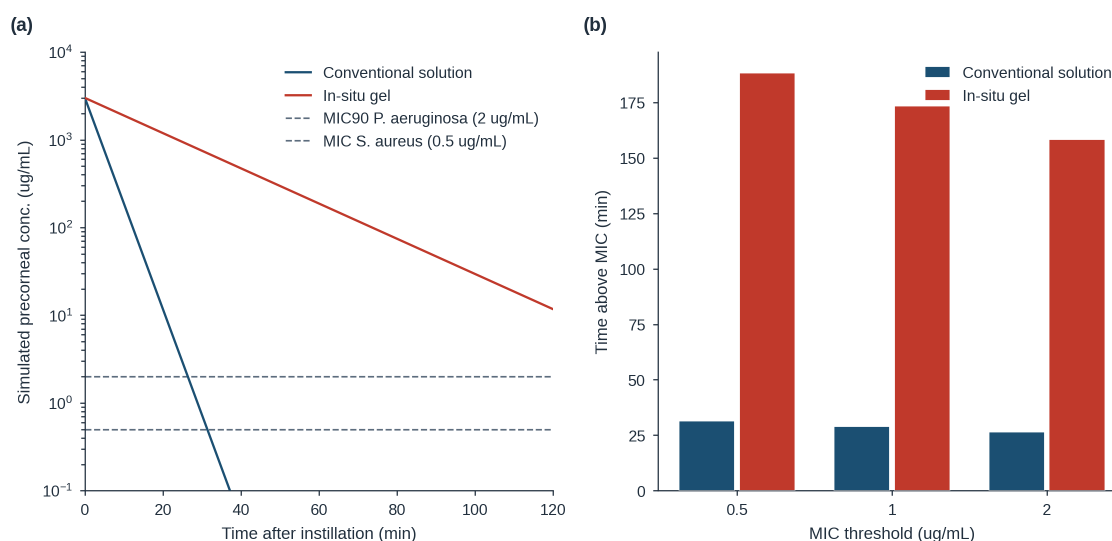
curve scales inversely with the rate constant, the precorneal exposure rose in the same proportion, a six-fold increase in the simulated area under the curve for the gel relative to the solution.

The pharmacodynamic consequence is summarised in Figure 2b and Table 3. Because the instilled concentration exceeds the inhibitory concentration of the target organisms by three to four orders of magnitude, the concentration remains above the inhibitory threshold for an appreciable time even for the fast-draining solution, but the gel extends that window substantially. For the conventional solution, the



simulated precorneal concentration stayed at or above 2  $\mu\text{g/mL}$ , the ninetieth-percentile inhibitory concentration for ocular *Pseudomonas aeruginosa*, for about 26 min. For the *in-situ* gel, the same threshold was maintained for about 158 min, a six-fold prolongation. The corresponding windows at 1  $\mu\text{g/mL}$  were about 29 min against about 173 min, and at 0.5  $\mu\text{g/mL}$  about 31 min against about 188 min. Across all three

thresholds the ratio between the gel and the solution was constant at six, which is a direct consequence of the model: with a shared starting concentration, the time above any threshold scales with the reciprocal of the elimination rate constant, so the fold improvement equals the ratio of the two half-lives regardless of which inhibitory concentration is chosen.



**Figure 2.** Simulated precorneal disposition of ciprofloxacin for a conventional solution and an *in-situ* gel, from a first-order precorneal elimination model with a common instilled concentration of 3000  $\mu\text{g/mL}$ . (a) Simulated precorneal concentration against time after instillation on a logarithmic concentration axis, with the reported ciprofloxacin minimum inhibitory concentration for *Staphylococcus aureus* (0.5  $\mu\text{g/mL}$ ) and the ninetieth-percentile value for ocular *Pseudomonas aeruginosa* (2  $\mu\text{g/mL}$ ) marked as horizontal thresholds. (b) Simulated time for which the precorneal concentration remained at or above each of three inhibitory thresholds, for the solution and the gel. All values are simulated, not measured.

**Table 3.** Simulated precorneal pharmacokinetic and pharmacodynamic parameters for a conventional ciprofloxacin solution and an *in-situ* gel, from a first-order precorneal elimination model with a common instilled concentration of 3000  $\mu\text{g/mL}$ .

| Parameter                                    | Conventional solution | In-situ gel |
|----------------------------------------------|-----------------------|-------------|
| Apparent precorneal half-life (min)          | 2.5                   | 15          |
| Apparent elimination rate constant (per min) | 0.277                 | 0.046       |
| Mean residence time (min)                    | 3.6                   | 21.6        |
| Relative precorneal AUC                      | 1.0                   | 6.0         |
| Time above MIC 0.5 $\mu\text{g/mL}$ (min)    | 31                    | 188         |
| Time above MIC 1 $\mu\text{g/mL}$ (min)      | 29                    | 173         |
| Time above MIC 2 $\mu\text{g/mL}$ (min)      | 26                    | 158         |

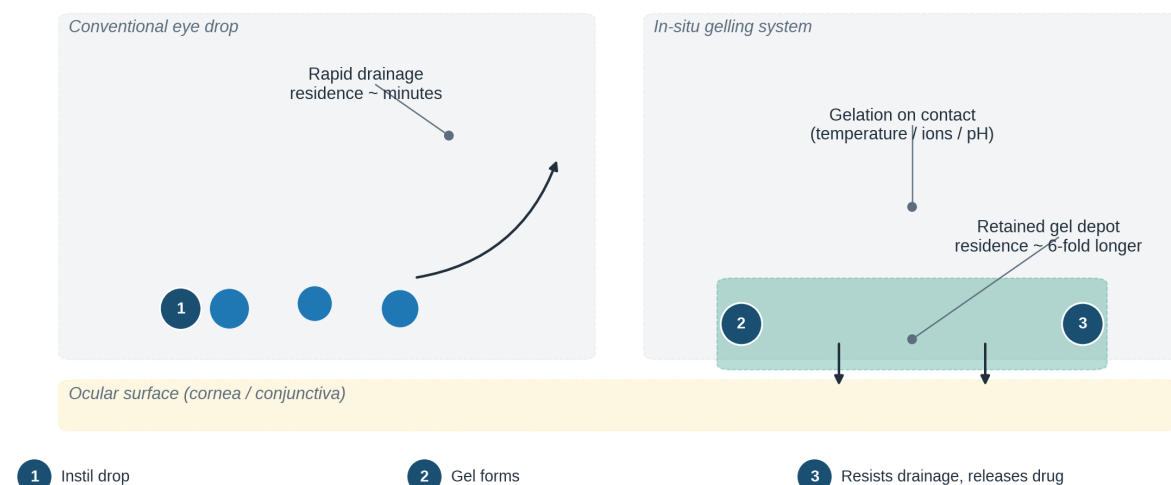


3.3 Published formulation, rheological and antibacterial evidence

Table 2. Reported formulation, rheological and performance data for ciprofloxacin and related fluoroquinolone in-situ ophthalmic gels.

| System and gelling polymer                 | Gelation trigger            | Gelation condition                            | Release behaviour                                                                                 | Reference    |
|--------------------------------------------|-----------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------|--------------|
| Poloxamer 407 (15-20%) with HPMC           | Temperature                 | Gels at about 30 degrees Celsius (optimised)  | About 40% at 30 min, about 83% over 8 h; residence about 60 min against about 10 min for solution | <sup>3</sup> |
| Carbopol 940 (0.03%) with HPMC K4M (0.05%) | pH                          | Gels on shift from acidic to neutral pH       | Sustained over 8 h; antibacterial efficacy comparable to commercial product                       | <sup>4</sup> |
| PVA (5-15%) and polymethacrylic acid       | Concentration and viscosity | Viscosity 54 to 1570 mPa s over the PVA range | Release half-time 307 min at 5% PVA, lengthening at higher fractions                              | <sup>5</sup> |
| Gellan gum (0.5%)                          | Ions (tear cations)         | Gels on contact with tear fluid               | Sustained over 8 h; effect prolonged toward 24 h                                                  | <sup>6</sup> |

The published formulation and performance data collected in Table 2, and the delivery concept for ciprofloxacin in-situ ophthalmic gels are they embody is drawn in Figure 3.



**Figure 3. Schematic of the in-situ gelling ophthalmic delivery concept. A conventional low-viscosity drop is cleared from the ocular surface by rapid lacrimal drainage within minutes, whereas an in-situ gelling system, instilled as a mobile liquid, undergoes a sol-to-gel transition on contact with the surface in response to temperature, tear ions or pH, forming a retained depot that resists drainage and releases drug over a prolonged period.**

The three gelation mechanisms are all represented. In the temperature-sensitive class, a poloxamer 407 system with hydroxypropyl methylcellulose as a viscosity modifier was reported to gel at an optimised temperature of 30

degrees Celsius, with the transition temperature falling from about 31.5 degrees Celsius toward 22 degrees Celsius as the polymer fraction was raised from 16.25 to 20 per cent; the optimised formulation released about 40 per cent of its



ciprofloxacin within 30 min and about 83 per cent over 8 h, against near-complete release of a marketed drop within 10 min, and it prolonged the ocular residence of the drug to about 60 min against about 10 min for the solution <sup>3</sup>. In the pH-sensitive class, a carbopol 940 system combined with hydroxypropyl methylcellulose K4M, optimised at 0.03 per cent carbomer with 0.05 per cent cellulose, gelled on the shift from the acidic formulation pH toward the neutral pH of tears and sustained release over 8 h, with an antibacterial efficacy reported as comparable to the commercial product <sup>4</sup>. In the ion-sensitive class, gellan gum systems gel on contact with the cations of the tear fluid; a gellan formulation at 0.5 per cent was shown to sustain fluoroquinolone-class release over 8 h and to prolong the pharmacodynamic effect toward 24 h<sup>6</sup>.

The rheological character common to these systems is a low viscosity before instillation and a marked rise on gelation, together with pseudoplastic, shear-thinning flow in the gel state, which allows the film to spread under the shear of a blink and to reform at rest. The dependence of viscosity on polymer concentration is steep. In a study of ciprofloxacin in polyvinyl alcohol and polymethacrylic acid vehicles, the viscosity of the polyvinyl alcohol solutions rose from 54 mPa s at 5 per cent to 238 mPa s at 7 per cent, 1313 mPa s at 10 per cent and 1570 mPa s at 15 per cent, and the in-vitro release slowed in step, the release half-time lengthening from 307 min at 5 per cent polyvinyl alcohol toward several thousand minutes at 15

per cent <sup>5</sup>. The antibacterial evidence across these systems is consistent in direction: the gelled formulations retained the intrinsic activity of ciprofloxacin against the ocular pathogens tested and, by holding the drug on the surface for longer, matched or exceeded the performance of the corresponding conventional drop. The inhibitory concentrations that this activity must exceed are modest. Ciprofloxacin was reported to have a ninetieth-percentile minimum inhibitory concentration of 2 µg/mL against ocular *Pseudomonas aeruginosa* isolates, with values ranging from 0.094 to 32 µg/mL across strains and a clinical susceptibility breakpoint at or below 1 µg/mL, and the 3 mg/mL commercial strength was effective in vitro against the strains tested <sup>7,10</sup>.

#### **4. Discussion**

The picture that emerges from the computed and the published evidence is coherent, and its logic is worth stating plainly. Ciprofloxacin is not a difficult molecule. Its calculated properties, a molecular weight of 331.35 g/mol, a calculated logP of 1.58, a polar surface area of 74.6 square angstroms and full compliance with four independent drug-likeness filters, describe a compact, well-behaved drug with no red flags of the kind that complicate permeation or stability. The obstacle to topical efficacy is not the drug but the eye, or more precisely the speed with which the eye clears anything placed on it. This reframing is the whole justification for an in-situ gelling vehicle, and the physicochemical profile earns its place in the argument by ruling out the alternative explanations. If the barrier were poor



permeability or an unfavourable partition, a residence-extending gel would help little; because the barrier is residence, a gel is aimed at exactly the right target.

The precorneal simulation puts a number on what that target is worth. Extending the apparent precorneal half-life from 2.5 to 15 min, a six-fold change consistent with the residence prolongation reported for a real poloxamer ciprofloxacin gel, raised the simulated exposure six-fold and lengthened the time above the *Pseudomonas* inhibitory concentration from about 26 min to about 158 min. For a bactericidal agent whose killing depends on the ratio of the achieved concentration to the inhibitory concentration and on the time that ratio is sustained, both of these gains are in the pharmacodynamically useful direction. A related and slightly counter-intuitive point falls out of the same model. Because the instilled concentration exceeds the inhibitory concentration by three to four orders of magnitude, the choice of inhibitory threshold barely moves the time-above-threshold window: the difference between the 0.5 and the 2  $\mu\text{g/mL}$  windows is a matter of a few minutes, whereas the difference the gel makes is a matter of two hours. The dominant lever is the residence time, not the potency margin, which is precisely the lever an in-situ gel pulls. It also implies that the practical benefit of prolonged residence is less about clearing an occasional resistant organism with a higher inhibitory concentration and more about reducing the dosing frequency needed to keep the surface continuously protected.

These computed findings sit comfortably beside the published formulation data. The reported poloxamer system gelled near the temperature of the ocular surface and slowed ciprofloxacin release from minutes to hours, the carbopol system converted the acidic-to-neutral pH shift of instillation into a gel that sustained release over eight hours, and the gellan systems used the tear cations to the same end. The rheological requirement that ties these together, low viscosity for instillation and a sharp, shear-thinning rise on gelation, is met by each mechanism through a different trigger, and the steep dependence of viscosity and release rate on polymer concentration seen in the polyvinyl alcohol and polymethacrylic acid series shows how directly the release rate can be tuned by formulation. The antibacterial reports, in turn, are consistent with the pharmacodynamic argument: a vehicle that keeps ciprofloxacin above its inhibitory concentration for longer should retain, and by prolonging exposure can extend, the antibacterial performance of the drug, and that is what the comparisons with conventional drops describe.

The limitations of this analysis are specific and should be read before its conclusions are extended. The precorneal model is a single-compartment, first-order description of a surface that is in reality heterogeneous and dynamic; it does not resolve the spreading of the film, the mixing with reflex tears, the partition into the corneal epithelium or the binding to mucin, and it treats the gel as a compartment with a slower drainage constant rather than as a swelling,



eroding matrix with its own release kinetics. The apparent half-lives that drive the model are literature-derived lumped parameters, and the six-fold prolongation assigned to the gel, though anchored to a reported residence comparison, will differ from formulation to formulation and from the animal or human surface on which it is measured. A simulated exposure is not a measured exposure, and the time-above-inhibitory-concentration figures should be read as the pharmacokinetic logic of the delivery strategy made quantitative, not as a prediction of clinical outcome. The physicochemical descriptors are calculated values with the usual model dependence of any such computation, and drug-likeness compliance speaks to developability, not to ocular efficacy. Most importantly, the antibacterial performance discussed here is drawn entirely from the cited experimental studies; no minimum inhibitory concentration, zone of inhibition or release percentage was generated in the present work, and the drug-likeness and pharmacokinetic computations do not and cannot substitute for a microbiological measurement.

Those limitations point to the experiments that would settle what the computation only frames. The natural next step is a rheological characterisation of a defined ciprofloxacin in-situ gel across the physiological trigger range, reporting the sol and gel viscosities, the gelation point and the shear-thinning index, paired with an in-vitro release study and a precorneal residence measurement in a suitable model, so that the assumed apparent half-life can be

replaced by a measured one and the simulation re-run against it. The antibacterial endpoint that matters is a time-kill study against *Pseudomonas aeruginosa* and *Staphylococcus aureus* ocular isolates comparing the gel with the conventional drop, because a time-kill curve tests the very quantity the simulation predicts the gel should improve, the duration of suprainhibitory exposure, in a way that a single zone-of-inhibition reading cannot. That is the bench week the present analysis argues is worth spending.

A further point deserves attention when the three gelation mechanisms are weighed against one another, because the choice carries real consequences for how the formulation behaves on a living surface. Temperature-triggered poloxamer systems gel reliably at the ocular surface but carry a large polymer load, typically fifteen to twenty per cent, which raises the tonicity and can leave a residue, and their gelation temperature is sensitive to the exact composition, so that a small error in polymer fraction shifts the transition into or out of the useful range. Ion-triggered gellan and alginate systems use very little polymer and gel sharply on contact with tears, which is attractive, but the strength of the resulting gel depends on the tear cation concentration, a quantity that varies between patients and with tear production, so the residence achieved in a healthy volunteer may not be reproduced in a dry or inflamed eye. pH-triggered carbomer systems convert the natural acidic-to-neutral shift of instillation into gelation with modest polymer, but the buffering capacity of the tears must overcome the buffering of the



formulation, and an over-buffered vehicle will not gel. None of these trade-offs is disqualifying, and each has been managed successfully for ciprofloxacin, but they explain why combinations, a thermogelling poloxamer stiffened by an ion-sensitive gellan, for instance, recur in the literature: a second trigger hedges against the failure mode of the first. The present pharmacokinetic argument is indifferent to which trigger is chosen, because it depends only on the residence time achieved, but the formulation that achieves a given residence most robustly across real ocular surfaces is the one worth carrying forward.

The dosing implication is the practical payoff and deserves to be made explicit. A conventional ciprofloxacin drop for an active corneal infection is given as often as every fifteen to thirty minutes in the first hours of treatment, a schedule that is punishing for the patient and poorly adhered to outside hospital. If an in-situ gel holds the surface concentration above the inhibitory threshold for roughly six times as long, the same protection could in principle be maintained with a proportionately less frequent schedule, which is exactly the kind of reduction that improves adherence and therefore real-world outcome. This inference must be read with the model's limits in mind, because time above the inhibitory concentration is a pharmacodynamic surrogate rather than a clinical endpoint, and the relationship between the two is not linear at the extremes. It is nonetheless the mechanism through which a residence-extending vehicle is expected to earn its clinical keep, and it is

measurable, which returns the argument once more to the bench.

## **5. Conclusion**

Ciprofloxacin is a compact, rule-compliant fluoroquinolone whose topical ocular limitation is residence rather than any property of the molecule, and an in-situ gelling vehicle is aimed squarely at that limitation. A precorneal simulation anchored to a reported residence prolongation indicates that a six-fold increase in apparent precorneal half-life translates into a six-fold increase in simulated ocular exposure and an extension of the time spent above the pseudomonal inhibitory concentration from roughly a quarter of an hour to well over two hours. Read together with the published formulation, rheological and antibacterial data for temperature-, pH- and ion-triggered ciprofloxacin gels, the analysis supports the pharmacokinetic rationale for an in-situ gelling ciprofloxacin system and identifies the rheological and time-kill experiments that would convert that rationale into evidence.

## **Declarations**

**Ethics approval.** This study involved no human participants, no animals and no biological specimens. It comprises computational analysis and a synthesis of previously published data, and required no ethics approval.

**Conflicts of interest.** The author declares no competing interests.

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