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IN SITU GELLING OPHTHALMIC SOLUTION OF MOXIFLOXACIN: RHEOLOGY AND OCULAR RETENTION

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Abstract

Topical moxifloxacin is widely used for bacterial conjunctivitis and keratitis, but a conventional eye drop is cleared from the precorneal area within minutes. In situ gelling solutions, which change from liquid to gel after instillation, are a proposed answer. This review summarises published work on the ocular barriers that shape retention, the polymers used to trigger gelation, the rheological measurements that describe both the instilled liquid and the resulting gel, and the methods used to judge residence time and release. Evidence for moxifloxacin itself is limited and mostly in vitro or in rabbits. The review reports no new data; it highlights inconsistent rheological reporting and the lack of human retention studies.

1. INTRODUCTION

Bacterial infections of the ocular surface are common, and most of them are treated with antibiotic drops. The convenience of a drop hides a poor delivery system. A typical instilled volume of 25 to 50 µL exceeds what the conjunctival sac can hold, much of the dose spills over the lid margin within seconds, and the rest is drained through the nasolacrimal duct at a rate set by tear turnover [1, 2, 3]. Only a small percentage of the dose crosses the cornea, which is why frequent dosing is the rule for topical anti-infectives [3, 4]. Patients often stop treatment early once symptoms ease, so the regimen needs to be simple enough to follow to the end of a course.

Fluoroquinolones have become first-line choices for many superficial infections because of their broad spectrum and good tissue penetration. Moxifloxacin, a fourth-generation agent, adds activity against Gram-positive organisms while retaining

Gram-negative cover, and it reaches useful concentrations in the aqueous humour after topical use [5, 6, 7]. A commercial 0.5% solution is available, but it still needs to be applied several times a day in the early stage of treatment. Missed doses and poor adherence are not rare, particularly in children and older patients, and sub-inhibitory exposure is the type of situation in which resistance develops [5, 8]. Cost matters too, since generic fluoroquinolone drops are cheap in many countries and any new vehicle must justify a higher price through real benefit.

Antibiotic resistance adds a further reason for caring about exposure. Fluoroquinolone resistance among ocular isolates, particularly staphylococci, has risen over the past two decades, and underdosing is thought to contribute by allowing resistant subpopulations to survive [5, 8]. A formulation that maintains a more even concentration at the ocular surface could, in principle, support effective therapy with fewer doses, though this has not been tested for resistance outcomes. The topic is raised here because it frames why retention is more than a convenience: shorter, better-controlled exposure is relevant to antimicrobial stewardship in primary care as well as in specialist ophthalmology [6, 8].

Making the drug stay longer in the eye is the logical response. Options have included viscous solutions, ointments, inserts, nanocarriers and in situ gelling systems [1, 9, 10]. The last group is attractive because it can be dispensed as an ordinary dropper bottle and changes consistency only once it meets the eye. This review brings together published evidence on in situ gelling moxifloxacin and closely related systems, with emphasis on two linked properties: rheology, which governs both the comfort of instillation and the strength of the gel, and ocular retention, which determines whether the design achieves its purpose. The review is narrative, and no new experimental results are reported.

A note on terminology helps. Some papers describe in situ gels as smart or stimuli-responsive carriers, and the triggers named are temperature, pH and ionic strength. Other authors use the same phrase for systems that rely on solvent exchange or photopolymerisation, which have mostly been used for parenteral depots rather than eye drops. Only the first three triggers are considered here, as they are the ones that have been seriously developed for topical ocular use [9, 11, 12]. Readers should note that the terminology is not used consistently across the literature.

2. OCULAR BARRIERS AND MOXIFLOXACIN

The ocular surface behaves as a series of dynamic barriers. The tear film, about 7 µL in volume in the normal human eye, is renewed at roughly 1 µL per minute, and a blink pushes excess liquid towards the puncta [13, 14]. Instilled solutions are diluted and removed with a half-life of a few minutes. Reflex tearing, triggered by an irritating formulation, speeds the process further, so a drop that stings is lost faster [14, 15]. The cornea then offers a lipophilic epithelium, a hydrophilic stroma and an endothelium, which together favour molecules with balanced lipophilicity [3, 16]. The small reservoir volume also means that every additional microlitre applied is largely wasted.

The ocular surface also clears drug by routes beyond simple drainage. Blinking, which occurs around fifteen times a minute in adults, squeezes the conjunctival sac and pumps tears towards the lacrimal puncta; the first minute after instillation removes the largest share of the dose [13, 15]. Part of the drug is absorbed non-productively through the conjunctiva into the systemic circulation, where it never reaches the aqueous humour. These losses mean that the volume of a drop, and the speed of the first blink, matter nearly as much as the concentration, and they explain why smaller drops, around 10 to 15 µL, have been suggested for improving efficiency in drug delivery [3, 14, 17].

Moxifloxacin is a zwitterion with a molecular weight of about 400 and moderate lipophilicity, a profile that suits corneal passage reasonably well. Clinical pharmacokinetic work showed that a 0.5% solution produces aqueous humour concentrations well above the minimum inhibitory concentration of most common

ocular pathogens within an hour or so [7, 18]. In vitro surveys of keratitis isolates have also shown low minimum inhibitory concentrations for moxifloxacin compared with older fluoroquinolones such as ciprofloxacin and ofloxacin [8]. These characteristics explain why the drug is a good candidate, though they do not remove the need for repeated dosing. Chelation could also reduce microbiological activity if the drug is bound in the gel before it reaches the cornea, a point few formulation papers examine.

Formulation constraints are specific. Fluoroquinolones chelate di- and trivalent cations, which matters when the gelling agent depends on ions. Solubility changes with pH, and moxifloxacin hydrochloride is soluble at the slightly acidic pH at which many pH-triggered polymers are supplied, but less soluble as the medium approaches neutrality, creating a risk of precipitation after gelation [6, 17]. The commercial product is a preservative-free isotonic solution at about neutral pH, and any gelling vehicle must keep comparable tonicity and avoid raising irritation [6, 19]. These limitations narrow the choice of polymer and buffer. A short course of anti-infective therapy may not expose the eye long enough to cause cumulative damage, but patients with chronic blepharitis or dry eye are different.

Tolerance is as important as pharmacokinetics for anti-infective drops, since a stinging formulation reduces adherence. Preservatives, buffer capacity, osmolality and the polymer itself all contribute to comfort. Benzalkonium chloride at the concentrations used in multidose bottles can damage the surface epithelium, and the effect accumulates with repeated use [20]. Formulation pH between about 6 and 8 is usually well tolerated, while tonicity within the range of roughly 250 to 350 mOsm/kg limits tearing [19]. A gelling vehicle adds viscosity and sometimes a slight residual film, so patient-reported comfort, not only slit-lamp findings, should be recorded [17, 20].

Preservatives deserve a separate mention. Benzalkonium chloride, the most common ophthalmic preservative, can damage the corneal and conjunctival epithelium with repeated use, and it also destabilises the tear film [20]. A formulation that reduces dosing frequency lowers cumulative preservative exposure, which is an argument for gelling systems in chronic conditions. For short courses of anti-infective therapy, the argument is weaker, and unit-dose designs may be simpler. Unit-dose containers avoid the problem but cost more and generate more packaging waste, which matters for large-volume public health use [19, 20]. Both options deserve evaluation in development.

3. GELLING MECHANISMS AND POLYMERS

The first practical in situ ocular gels used pH change. Carbomer is supplied as an acidic dispersion with low viscosity, and when it meets tear fluid at about pH 7.4 the carboxyl groups ionise, the chains repel each other and the dispersion thickens abruptly [9, 21]. Srividya and colleagues applied this principle to ofloxacin, combining carbomer with hydroxypropyl methylcellulose to increase gel strength and lower the amount of carbomer needed [9]. The weakness of the approach is the acidic vehicle, which can irritate and which the small buffering capacity of tears may not neutralise completely, so gelation is variable between users [21, 22]. Eye drops containing carbomer have been in use for dry eye for many years, which supports its general tolerability.

Ionic gelation exploits the cations in tears, mainly sodium, potassium and calcium. Gellan gum, an anionic polysaccharide, forms a firm gel at low polymer concentration when its helices associate in the presence of these ions, and the commercial timolol gel based on it showed that such a system could be accepted by patients and regulators [12, 23]. Sodium alginate behaves similarly in the presence of calcium, with gel strength depending on its guluronic acid content [10]. Balasubramaniam and Pandit used a gellan system for ciprofloxacin and reported sustained release in vitro and longer action than a plain solution [12]. For fluoroquinolones the possibility of binding to cations needs checking case by case.

Thermosensitive systems rely on polymers whose solution is liquid at room temperature but gels near the temperature of the ocular surface, about 32 to 35 °C. Poloxamer 407, a triblock copolymer of polyoxyethylene and polyoxypropylene, is the most studied example. Aqueous solutions of roughly 20% or more gel as micelles pack together when the temperature rises [24]. Poloxamer was applied to ophthalmic use as early as the 1980s in a pilocarpine study [25]. Its drawbacks are the high concentration required, which makes the gel weak and rapidly eroding, and the sensitivity of the gelation temperature to additives, including drugs and salts [26].

Combinations are therefore the norm. Poloxamer with a mucoadhesive polymer such as carbomer, hydroxypropyl methylcellulose or chitosan lowers the poloxamer concentration needed and raises the gel's adhesion; a Carbopol and Pluronic system gave sustained release of pilocarpine with a less demanding total polymer load [27, 28]. Dual-trigger designs, sensitive to both temperature and ions or pH, can compensate for the weakness of either alone. The price is complexity: more variables to optimise, and more ways for batches to differ [11, 29]. The molecular weight and degree of substitution of cellulose derivatives also influence the viscosity and strength of the final mixture, so batch-to-batch variation in the polymer is not a trivial matter. Published comparisons of grades are rare.

The main approaches reported for fluoroquinolones and related ocular drugs are brought together in table 1, grouped by the gelling trigger that each uses. A few observations follow from the table. Ion-activated and pH-triggered systems dominate the antibiotic literature, thermosensitive poloxamer gels predominate for older model drugs such as pilocarpine, and moxifloxacin itself is represented by only a handful of reports [9, 12, 24, 25, 27, 30]. The distribution of entries by trigger or evidence type is shown in fig. 1. The relative absence of retention measurements in moxifloxacin work, compared with other drugs, is noticeable, and the limited characterisation studies are mostly borrowed from other mucosal gels [7, 31].

A moxifloxacin-specific study used a pH- and ion-sensitive combination and reported prolonged in vitro release with acceptable clarity and no irritation in an ocular test, concluding that the gel could reduce dosing frequency [30]. Other authors have investigated moxifloxacin in nanoparticle suspensions or in chitosan matrices. The available papers are small and heterogeneous, which prevents a quantitative comparison, but they agree on the basic pattern that gelation extends release compared with the solution [11, 29, 30]. Few moxifloxacin studies describe the effect of the buffer on the gel. Few moxifloxacin studies describe the effect of the buffer on the gel, or on the stability of the drug within it.

Several factors set the final strength of the gel in the eye. The polymer concentration is the obvious one, but the dilution by tears, the local ion content, and the presence of drug and buffer salts matter as well [22, 27]. Mucoadhesive polymers such as carbomer, chitosan and hyaluronate interact with mucin through hydrogen bonding and electrostatic attraction, which anchors the gel to the ocular surface and slows its removal by blinking, though it may also make the system feel sticky or cause lid crusting [22, 32]. Designers have to balance these gains against comfort. In practice a gel with moderate strength and good adhesion is preferred to one that is stiff and sits as a foreign body. Reports using these systems also seldom state the drug loading, which limits comparison.

4. RHEOLOGICAL CHARACTERISATION

Rheology is central to design because the formulation has two lives. As a liquid it must pour from a dropper, spread across the cornea and cause no discomfort; as a gel it must resist the shear of blinking, which is high and brief, while remaining soft enough not to blur vision [33]. Both states can be described by controlled-rate and oscillatory measurements. Flow curves show whether the sol is Newtonian or shear-thinning, and oscillatory tests give the storage modulus G′ and loss modulus G″ that separate elastic from viscous behaviour [34, 35]. Rheological reports

should therefore describe both states, and the transition between them.

Shear rate is the variable most often forgotten. During a blink the lid sweeps across the cornea at rates that have been estimated in the order of thousands of reciprocal seconds, while the open eye between blinks imposes very little shear [33, 34]. A formulation that is thick at rest and thins under blinking would protect against drainage between blinks and still feel smooth. Pure Newtonian vehicles cannot do this, which is one reason for the interest in polysaccharide and carbomer-based systems. Measurements across a wide range of shear rates, from about 0.1 to 1000 s−1, would therefore reveal more than the single-speed viscometer readings that appear in many formulation papers [31, 35].

Table 1: Published in situ gelling approaches for fluoroquinolones and related ocular drugs, with rheology and retention findings

System / drug	Principal reported finding	Ref.
Carbomer + HPMC ofloxacin	pH-triggered gel gave sustained release in vitro; HPMC raised gel strength	[9]
Carbopol + Pluronic pilocarpine	Phase-change solution prolonged release with lower total polymer	[27]
Gellan gum ciprofloxacin	Ion-activated gel sustained release and action compared with a solution	[12]
Alginate general	Gelation by calcium in tears; strength depends on guluronic acid content	[10]
Poloxamer 407 pilocarpine	Thermogel increased miotic response versus aqueous solution in rabbits	[25]
Thermosetting gel scintigraphy	Longer corneal residence than solution when gelation temperature was tuned	[24]
Mucoadhesive gel vaginal model	Dilution with simulated fluid shifted gelation temperature and rheology	[31]
Viscosity in rabbit and man solutions	Viscosity effect on residence differs between species	[14]
Moxifloxacin in situ gel	Prolonged in vitro release with good clarity and no irritation in rabbits	[30]
Moxifloxacin 0.5% human	Aqueous humour concentrations above MIC of common pathogens after topical use	[7]

For the pre-gel state, a low viscosity of the order of tens of millipascal seconds is generally preferred, enough for a drop to be accurately metered. Shear-thinning is helpful because it lets the liquid thin as it leaves the nozzle and the lid wipes it across the eye [33]. Studies of ocular viscosity have shown that raising viscosity prolongs precorneal residence, but only up to a point; very viscous solutions blur vision and are not necessarily retained better than moderately thick ones [14, 15]. Viscosity thus has to be tuned and not simply maximised. The sharpness of the transition is itself important, because a gel that forms gradually over many minutes may drain before it has set.

For the gel state, temperature sweeps at a constant frequency identify the gelation temperature as the point at which G′ crosses G″, and the sharpness of the transition is a design feature [31, 34]. Chang and colleagues examined thermosensitive mucoadhesive gels under physiologically relevant conditions and demonstrated that dilution with simulated fluid shifts the transition, an effect that bears directly on eyes with only microlitres of tears [31]. Frequency sweeps tell whether the gel behaves as a true network, with G′ above G″ and little dependence on frequency, or as an entangled solution that will flow under prolonged stress [34, 35].

Practical measurement choices influence the numbers. The gap between plates, the geometry (cone and plate or parallel plate), the strain amplitude and the temperature control all alter results, particularly for weak gels where the linear viscoelastic region is narrow [34, 35]. Amplitude sweeps should therefore precede frequency sweeps, so that tests are run within the region in which the structure is not being destroyed. Thermosensitive samples need a controlled heating rate, as a faster ramp pushes the apparent gelation point upward. Papers that give only a single viscosity figure at an unspecified shear rate are of little use for

comparison with other work [31, 33].

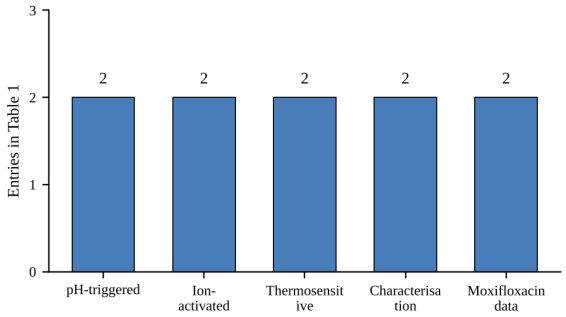


Fig. 1: Number of entries in table 1 by gelling trigger or evidence type

Mucoadhesion is often judged rheologically through rheological synergism, the extra viscosity seen when a polymer is mixed with mucin. The method is easy to apply but strongly influenced by the polymer, mucin source, pH and ionic strength, so values from different laboratories are hard to compare [27, 32]. Texture analysis and tensile detachment tests provide mechanical measures of adhesion, and more direct evidence needs imaging of the formulation on tissue [22, 27]. Several investigators advise combining at least two of these measures instead of relying on a single one. The point is simple: a number without conditions cannot be reproduced.

A recurring issue is that rheology is measured at conditions unlike the eye. Standard rheometers use millilitre volumes at a controlled temperature, while the eye offers a few microlitres at a fluctuating surface temperature, mixing with tears that dilute the polymer and change the ion content [31]. Experiments in which gel is mixed with simulated tear fluid in a realistic ratio, typically about 25 parts of formulation to 7 of fluid, provide a more reasonable test and should be routine [28, 31]. Standardised artificial tear compositions, such as those used for in vitro release tests, are readily available and should be specified.

5. ASSESSING OCULAR RETENTION AND RELEASE

Retention is measured in three ways, each with its own weakness. Gamma scintigraphy follows a radiolabelled formulation over time and gives the most direct non-invasive picture of precorneal clearance in animals and people [14, 15]. Fluorescein-labelled preparations can be viewed on the cornea with a slit lamp or imaged, which is cheaper but less quantitative. Drug concentration in tears or aqueous humour after instillation is the third route, and the most clinically relevant, but it requires sampling that is invasive in humans [7, 18]. Wei and colleagues used scintigraphy to show that a thermosetting gel remained on the rabbit cornea considerably longer than a solution [24].

Rabbits dominate the literature. Their eyes are convenient, but the blink rate is low and the tear volume and turnover differ from those in people, so clearance is slower and gel advantages may look larger than they would clinically [14, 15, 36]. Zaki and co-workers compared the effect of viscosity on residence in rabbit and man and found a clear difference between the two, which is a caution for anyone extrapolating retention times [14]. Human data for in situ gels are limited to a small number of products and short studies, and for moxifloxacin none have been published to the best of the available literature [23].

The link between residence and drug concentration is not linear. Early work on pilocarpine in rabbits showed that a longer contact time raises corneal penetration, but only until the corneal membrane becomes the limiting step, after which additional residence adds little [16, 36]. Moxifloxacin passes the cornea reasonably readily, so the possible gain from long residence is larger than for a poorly permeating drug, yet it is still bounded. Estimates of fractional ocular bioavailability for topical drugs remain in the low single digits even for good formulations, and a gel that doubles it still delivers a small share of the dose [3, 17]. That perspective should temper the language of claims.

In vitro release testing is the usual first step. Franz diffusion cells with a membrane, or dialysis arrangements, measure the drug entering a receptor medium of simulated tear fluid, with sampling over hours [12, 28]. Data are then fitted to kinetic models: zero-order, first-order, Higuchi's square-root-of-time relation, and the Korsmeyer–Peppas power law whose exponent hints at diffusion or erosion control [37, 38, 39]. Model fitting should be used cautiously, because many curves fit several models and a high

correlation coefficient alone does not prove a mechanism [39]. For instance, a gel may release drug slowly into the receptor chamber because the membrane is the limiting step, not the gel.

The conclusions that can be drawn from release data are limited by the sink conditions imposed. In a Franz cell the receptor fluid is large and constantly stirred, while in the eye the gel faces a thin, slowly renewed film. A formulation that appears to release over eight hours in vitro may be eroded and drained in a shorter time in the eye, or may last longer. In vitro studies are best viewed as a way to rank candidate formulations rather than to predict residence in patients [12, 28, 36]. Minimum inhibitory concentrations of the test strains should be stated, so that the zone sizes can be interpreted.

A few studies relate release to antimicrobial effect, using agar diffusion or time-kill assays against Staphylococcus aureus and Pseudomonas aeruginosa. Zones of inhibition from gels are generally similar to or slightly larger than those of solutions with the same drug content, which shows that the gel matrix does not inactivate the drug, but it does not demonstrate better clinical effect [12, 30]. Reports should also state the frequency of sampling. Reports should also state the frequency of sampling, the volume of the receptor medium and whether sink conditions were maintained throughout the test, since these details change the shape of the profile.

6. SAFETY, QUALITY AND REGULATORY POINTS

Ophthalmic products must be sterile, free from particulate matter, appropriately buffered and isotonic, and the quality attributes specific to gels include clarity, gelation temperature or pH, viscosity and content uniformity [19, 40]. Sterilisation is a particular difficulty because autoclaving can change polymer properties; thermosensitive polymers may be sterile-filtered in the cold and carbomer or gellan systems may need heat sterilisation with revalidation of rheology afterwards [23, 26]. Stability studies under regulatory conditions should include rheological parameters, not only assay and degradation products [41]. Container design, filling conditions and the closure system also influence sterility assurance in multidose bottles.

Compendial standards give a starting framework. The European Pharmacopoeia requires ophthalmic preparations to be sterile, to be prepared so as to minimise contamination and particulate matter, and to include a suitable preservative in multidose containers unless the formulation itself is adequately protected [40]. Combinations of carbomer and poloxamer have been studied specifically to cut the polymer load needed for gelation while keeping the solution pourable and easy to instil [27]. For gels these general requirements are supplemented by product-specific tests, because dose uniformity from a viscous or gelling liquid cannot be assumed. Delivered drop volume, drop number per container and the force needed to squeeze the bottle are practical parameters that deserve inclusion in development reports [19, 40].

Tolerability is assessed with the classic Draize eye test, still cited widely, or with alternatives such as the hen's egg chorioallantoic membrane test and cell-based assays [42]. Studies of in situ gels generally report no ocular irritation in rabbits at the doses tested, but the numbers are small and the observation periods short [12, 30, 42]. Vision is the main patient concern: a gel that is cloudy or leaves a film can blur sight for several minutes, and acceptance of ophthalmic gels in practice depends on this as much as on pharmacokinetics [23, 33]. Hospital pharmacists compounding gels from raw materials face the extra burden of validating sterility and rheology themselves.

Some practical points arise for pharmacy practice. Patients need to shake or not shake the bottle as directed, avoid touching the dropper to the eye, and wait about five minutes between different eye drops, since a second drop can wash out a gel before it has had time to form [1, 19]. Storage guidance can be specific, because thermosensitive systems may gel prematurely if kept in a warm place. Labelling and counselling matter for these products more than for simple solutions [23, 40]. A short instruction leaflet for patients is a cheap and sensible addition.

7. LIMITATIONS AND FUTURE DIRECTIONS

The evidence base for moxifloxacin in situ gels has several gaps. Published formulation papers seldom report full rheological conditions, such as temperature, shear rate, frequency and the dilution used, so results cannot be compared [34]. Animal retention studies rely on rabbits, and few use a validated quantitative method. Antimicrobial and clinical outcomes are almost never measured [11, 29, 30]. Finally, many reports test a single optimised formulation without a commercial solution as a reference, which makes an advantage hard to judge. Put simply, these gaps explain why strong claims are premature.

Clinical translation would require a deliberately modest first step. A small crossover study in healthy volunteers, comparing the gel with the marketed solution, could measure tear concentrations of moxifloxacin at fixed times after a single drop, together with comfort and visual acuity scores. Such a design needs few participants, carries little risk and would show at once whether the extra residence seen in animals is reproduced in people [7, 14, 18]. Only if it did would a trial in patients with bacterial conjunctivitis be justified, with clinical cure as the primary outcome and a non-inferiority margin agreed beforehand, since the realistic aim is equal efficacy with fewer instillations and not superior efficacy [5, 23]. Shared protocols would also make meta-analysis possible, which is currently out of reach.

A more convincing programme would define target product characteristics at the start, including drop size, viscosity before and after gelation, and desired residence time. It would test candidates with realistic tear dilution, use a validated imaging or scintigraphic method in rabbits, and include a bridging human study of retention in healthy eyes before efficacy trials [14, 24, 31]. Standard reporting of rheological conditions would help later reviewers pool evidence. Pharmaceutical scientists and ophthalmologists would both gain from such shared protocols. Cost and manufacturing complexity will decide whether any of them reach the pharmacy shelf.

Newer ideas, among them nanoparticle-laden gels, cyclodextrin complexes, and contact lens or insert-based delivery, will compete for attention, and some may prove better suited to chronic disease than a gel is to short antibiotic courses. A fair comparison between these approaches will need common endpoints [10, 11, 29]. For acute infections that resolve within days, the benefit of a gel is mostly reduced dosing frequency, and this needs to be weighed against cost and any effect on vision. None of this is unique to moxifloxacin, and lessons from other drug classes should be borrowed freely.

8. CONCLUSION

In situ gelling vehicles offer a realistic way to prolong the ocular contact of moxifloxacin, and the formulation principles are well established from work on pilocarpine, ofloxacin, ciprofloxacin and timolol [9, 12, 23, 25]. Rheology links the design to its function: a low-viscosity, shear-thinning sol that gels sharply and to an adequate strength at eye conditions is the target, and that target is best verified with realistic tear dilution [31, 34]. The reported formulations differ in trigger, polymer and test conditions, which makes the field look more coherent than it is.

What is missing is proof in the setting that matters. Retention data for moxifloxacin gels are scarce, rabbit models overstate clearance times, and human studies are absent [14, 30]. Before clinical claims are made, laboratories should report rheological conditions fully, quantify retention by a validated method and compare against the marketed solution. Until then, in situ moxifloxacin gels remain a reasoned but unproven improvement on the drop [11, 29]. Collaboration between formulation scientists and ophthalmologists would speed this up.

9. ABBREVIATIONS

G′-Storage modulus, G″-Loss modulus,
HPMC-Hydroxypropyl methylcellulose,
ICH-International Council for Harmonisation,
MIC-Minimum inhibitory concentration,
pH-Negative logarithm of hydrogen ion activity

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11. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

12. CONFLICT OF INTERESTS

Declared none

13. REFERENCES

1. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J 2010;12:348–60.
2. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. World J Pharmacol 2013;2:47–64.
3. Urtti A. Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv Drug Deliv Rev 2006;58:1131–5.
4. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv 2006;3:275–87.
5. Miller D. Review of moxifloxacin hydrochloride ophthalmic solution in the treatment of bacterial eye infections. Clin Ophthalmol 2008;2:77–91.
6. Mather R, Karenchak LM, Romanowski EG, Kowalski RP. Fourth generation fluoroquinolones: new weapons in the arsenal of ophthalmic antibiotics. Am J Ophthalmol 2002;133:463–6.
7. Hariprasad SM, Blinder KJ, Shah GK, *et al.* Penetration pharmacokinetics of topically administered 0.5% moxifloxacin ophthalmic solution in human aqueous and vitreous. Arch Ophthalmol 2005;123:39–44.
8. Kowalski RP, Dhaliwal DK, Karenchak LM, *et al.* Gatifloxacin and moxifloxacin: an in vitro susceptibility comparison to levofloxacin, ciprofloxacin, and ofloxacin using bacterial keratitis isolates. Am J Ophthalmol 2003;136:500–5.
9. Srividya B, Cardoza RM, Amin PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J Control Release 2001;73:205–11.
10. Cohen S, Lobel E, Trevgoda A, Peled Y. A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye. J Control Release 1997;44:201–8.
11. Agrawal AK, Das M, Jain S. In situ gel systems as 'smart' carriers for sustained ocular drug delivery. Expert Opin Drug Deliv 2012;9:383–402.
12. Balasubramaniam J, Pandit JK. Ion-activated in situ gelling systems for sustained ophthalmic delivery of ciprofloxacin hydrochloride. Drug Deliv 2003;10:185–91.
13. Mishima S, Gasset A, Klyce SD, Baum JL. Determination of tear volume and tear flow. Invest Ophthalmol 1966;5:264–76.
14. Zaki I, Fitzgerald P, Hardy JG, Wilson CG. A comparison of the effect of viscosity on the precorneal residence of solutions in rabbit and man. J Pharm Pharmacol 1986;38:463–6.
15. Chrai SS, Patton TF, Mehta A, Robinson JR. Lacrimal and instilled fluid dynamics in rabbit eyes. J Pharm Sci 1973;62:1112–21.
16. Sieg JW, Robinson JR. Mechanistic studies on transcorneal permeation of pilocarpine. J Pharm Sci 1976;65:1816–22.
17. Lang JC. Ocular drug delivery conventional ocular formulations. Adv Drug Deliv Rev 1995;16:39–43.
18. Robertson SM, Curtis MA, Schlech BA, Rusinko A. Ocular pharmacokinetics of moxifloxacin after topical treatment of animals and humans. Surv Ophthalmol 2005;50(Suppl 1):S32–45.
19. Bartlett JD, Jaanus SD, eds. Clinical Ocular Pharmacology. 5th ed. Boston: Butterworth-Heinemann; 2008.
20. Baudouin C, Labbé A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res 2010;29:312–34.
21. Gupta H, Jain S, Mathur R, Mishra P, Mishra AK, Velpandian T. Sustained ocular drug delivery from a temperature and pH triggered novel in situ gel system. Drug Deliv 2007;14:507–15.
22. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Deliv Rev 2005;57:1595–639.
23. Almeida H, Amaral MH, Lobão P, Lobo JMS. In situ gelling systems: a strategy to improve the bioavailability of ophthalmic pharmaceutical formulations. Drug Discov Today 2014;19:400–12.
24. Wei G, Xu H, Ding PT, Li SM, Zheng JM. Thermosetting gels with modulated gelation temperature for ophthalmic use: the rheological and gamma scintigraphic studies. J Control Release 2002;83:65–74.
25. Miller SC, Donovan MD. Effect of poloxamer 407 gel on the miotic activity of pilocarpine nitrate in the rabbit eye. Int J Pharm 1982;12:147–52.
26. Dumortier G, Grossiord JL, Agnely F, Chaumeil JC. A review of poloxamer 407

pharmaceutical and pharmacological characteristics. Pharm Res 2006;23:2709–28.

27. Lin HR, Sung KC. Carbopol/pluronic phase change solutions for ophthalmic drug delivery. J Control Release 2000;69:379–88.
28. Rupenthal ID, Green CR, Alany RG. Comparison of ion-activated in situ gelling systems for ocular drug delivery. Part 1: physicochemical characterisation and in vitro release. Int J Pharm 2011;411:69–77.
29. Wu Y, Liu Y, Li X, *et al.* Research progress of in-situ gelling ophthalmic drug delivery system. Asian J Pharm Sci 2019;14:1–15.
30. Mandal S, Thimmasetty MK, Prabhushankar GL, Geetha MS. Formulation and evaluation of an in situ gel-forming ophthalmic formulation of moxifloxacin hydrochloride. Int J Pharm Investig 2012;2:78–82.
31. Chang JY, Oh YK, Choi HG, Kim YB, Kim CK. Rheological evaluation of thermosensitive and mucoadhesive vaginal gels in physiological conditions. Int J Pharm 2002;241:155–63.
32. Greaves JL, Wilson CG. Treatment of diseases of the eye with mucoadhesive delivery systems. Adv Drug Deliv Rev 1993;11:349–83.
33. Zignani M, Tabatabay C, Gurny R. Topical semi-solid drug delivery: kinetics and tolerance of ophthalmic hydrogels. Adv Drug Deliv Rev 1995;16:51–60.
34. Barnes HA, Hutton JF, Walters K. An Introduction to Rheology. Amsterdam: Elsevier; 1989.
35. Mezger TG. The Rheology Handbook. 2nd ed. Hannover: Vincentz Network; 2006.
36. Lee VHL, Robinson JR. Mechanistic and quantitative evaluation of precorneal pilocarpine disposition in albino rabbits. J Pharm Sci 1979;68:673–84.
37. Siepmann J, Siepmann F. Mathematical modeling of drug delivery. Int J Pharm 2008;364:328–43.
38. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv 1985;60:110–1.
39. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm 2010;67:217–23.
40. European Directorate for the Quality of Medicines. European Pharmacopoeia. Ophthalmic preparations. Strasbourg: Council of Europe; 2020.
41. Bajaj S, Singla D, Sakhuja N. Stability testing of pharmaceutical products. J Appl Pharm Sci 2012;2:129–38.
42. Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944;82:377–90.