Expert Opinion

Controlled transscleral drug delivery formulations to the eye: establishing new concepts and paradigms in ocular anti-inflammatory therapeutics and antibacterial prophylaxis

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Importance of the field: The use of topical agents poses unique and challenging hurdles for drug delivery. Topical steroids effectively control ocular inflammation, but are associated with the well-recognized dilemma of patient compliance. Although administration of topical antimicrobials as prophylaxis is acceptable among ophthalmologists, this common practice has no sound evidence base. Developing a new antimicrobial agent or delivery strategy with enhanced penetration by considering the anatomical and physiological constraints exerted by the barriers of the eye is not a commonly perceived strategy. Exploiting the permeability of the sclera, subconjunctival routes may offer a promising alternative for enhanced drug delivery and tissue targeting.
Area covered in this review: Ocular drug delivery strategies were reviewed for ocular inflammation and infections clinically adopted for newer class of antimicrobials, which use a multipronged approach to limit risks of endophthalmitis.
What the reader will gain: The analysis substantiates a new transscleral drug delivery therapeutic approach for cataract surgery.
Take home message: A new anti-inflammatory and anti-infective paradigm that frees the patient from the nuisance of topical therapeutics is introduced, opening a large investigative avenue for future improved therapies.

1. Introduction

Topical steroids effectively control ocular inflammation [1,2], but are associated with the well-recognized challenge of patient compliance [3]. A pellet shape made of copolymers of lactic and glycolic acids (also known as poly(lactic-*co*-glycolic) acid, poly(lactide-*co*-glycolide) intraocular dexamethasone delivery system) has previously been suggested; however, there is no evidence to support its routine clinical acceptance [4-7]. Injection of depot corticosteroids into sub-Tenon's capsule is an

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Article highlights.

- The use of topical agents poses unique and challenging hurdles for drug delivery.
- In parallel with new drugs development, controlled drug delivery which explores the routes of transscleral delivery thereby and circumventing the cornea-conjunctival barriers may be key to an ultimate anti-infective and anti-inflammatory strategy with enhanced tissue targeting.
- Sustained drug delivery devices offer an excellent alternative to solve many problems associated with patient use of postoperative drops after cataract surgery.
- By bridging the potential of late-generation antimicrobials and anti-inflammatory drugs to the need for focused and engineered pharmacologic intervention in cataract surgery, transscleral delivery of biodegradable microparticles sits at the crossroad of patient comfort, treatment compliance and enhanced protection.

This box summarizes key points contained in the article.

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established approach for treating various ocular inflammatory diseases [8-10]. Its prolonged therapeutic effect has provided the ophthalmologist with an alternative tool for the treatment of different diseases [11-16] that may be extended to the surgical arena to modulate postoperative inflammation [17,18].

The use of topical antimicrobials agents poses unique and challenging hurdles for drug delivery, especially because recent reports have suggested that the incidence of endophthalmitis may be increasing [19,20]. The European clinical trial (ESCRS Endophthalmitis Study Group) [21] has shown that high intraocular antimicrobial levels are key to patient protection. Exploiting the permeability of the sclera, subconjunctival routes may offer a more promising alternative for enhanced drug delivery and tissue targeting compared with topical routes [22-27]. Clinical reports also have associated subconjunctival antimicrobials administered during routine intraocular surgery with better outcomes [28-30]. In theory, the combination of an antimicrobial with a steroid in a controlled release system delivered transsclerally could be feasible after cataract surgery to achieve several clinical objectives: eliminate topical medications, enhance patient compliance and improve drug bioavailability.

A fundamental understanding of the absorption, distribution and elimination pathways for delivery of drugs into the eye is required for rational treatment paradigms. The anatomic and physiologic barriers of the eye render drug delivery to the anterior and posterior segment tissues a major challenge. Anterior entry of xenobiotics through the cornea is blocked by an efficient biomembrane structure comprised of hydrophobic epithelium followed by hydrophilic stroma, where the accessibility of both water-insoluble and water-soluble compounds into the aqueous humor is restricted to a high extent. The aqueous bioavailability of most of the topically applied eye drops is < 5% of the applied dosage.

Subconjunctival ocular drug delivery represents an attempt to elevate intraocular drug concentrations and minimize the frequency of dosing. Compared with direct intraocular injection, this approach is less risky to the patient and less invasive. As the sclera is much more permeable than the conjunctiva, the formidable permeability barrier consisting of both cornea and conjunctiva can be avoided altogether with such a route. The advantage of subconjunctival implants as opposed to subconjunctival injection of solution is the achievement of higher drug concentrations and sustained release of drug into both aqueous and vitreous humor [31-33].

In parallel with antimicrobial development, controlled drug delivery that explores the routes of transscleral delivery, thereby circumventing the cornea–conjunctival barriers, may be key to an ultimate anti-infective strategy. Therefore, the encouraging preliminary results prompted the authors' group to explore this hypothesis in a controlled trial of one intraoperative sub-Tenon's capsule injection of triamcinolone and ciprofloxacin in a biodegradable controlled release system compared with conventional postoperative prednisolone and ciprofloxacin eye drops, to treat ocular inflammation and for infection prophylaxis after cataract surgery. A new and more comprehensive anti-inflammatory and anti-infective strategy that frees the patient from the nuisance and expense of topical therapeutics and potentially enhances intraocular drug bioavailability has been introduced [34]. In support, the feasibility of this biodegradable transscleral drug delivery system has been experimentally tested as an anti-infective prophylaxis approach. The drug tolerance and intraocular bioavailability of one subconjunctival injection of 2 mg ciprofloxacin loaded in a controlled release microspheres system was compared with one subconjunctival injection of 2 mg ciprofloxacin in its free form to 0.3% ciprofloxacin eye drops using a dosing regimen that simulated prophylactic use following cataract surgery. The study also investigated the potential of these two different approaches of ciprofloxacin delivery to prevent bacterial endophthalmitis when the anterior chamber was challenged with *Staphylococcus aureus* [35].

This review, therefore, focuses on results from recent developments of the authors' group (Brazilian Ocular Pharmacology and Pharmaceutical Technology Research Group) attempting to improve postoperative anti-inflammatory control in cataract surgery and to increase antimicrobial penetration across the cornea and ocular barriers.

2. Transscleral sustained released drugs for cataract surgery

2.1 Technological approaches of micro- and nanoparticles for ocular transecleral drug delivery

Research and development in the pharmaceutical technology area has introduced an increasing number of therapeutic possibilities for medical treatment of many diseases, especially the ocular diseases. The field of controlled drug release represents a frontier area in medical science. The systems offer clear

Table 1. Comparative strategy for antimicrobials in targeting zero incidence of endophthalmitis.

Potential protective characteristics	Type of delivery		
	Eye drops	Intracameral	Transscleral controlled drug delivery
Contamination from the surface of the eye	High protection	No protection	High protection
Aqueous humor concentration	Low concentration	High concentration	Moderate concentration
Vitreous humor concentration	No detection	Moderate concentration	Low concentration
Sustainable therapeutical levels	Low therapeutical levels depending on patient compliance	Short protective effect (probably < 24 h)	Sustained intraocular therapeutical levels up to 10 days, and do not depend on patient treatment compliance

advantages compared with conventional drug dosage forms, such as increasing the drug efficiency, reduced toxicity, increased patient compliance, improved safety and patient comfort [36].

Sustained drug delivery devices offer an excellent alternative to solve many problems associated with patient use of drops after cataract surgery. These devices are made either from biostable (non-biodegradable, non-erodible), or from biodegradable (erodible) polymers. The erodible devices have an inherent advantage over the non-erodible systems in that as they degrade, they gradually disappear from the site of implantation. The particles consist of drugs entrapped within a polymer, and are frequently classified by size into microparticles (> 1 μm) and nanoparticles (< 1 μm). By physical structure, the microparticles are classified as microspheres and microcapsules. Microcapsules have a drug core surrounded by a polymeric film, whereas in the microspheres the drug is dispersed through the polymeric matrix. The aim in the development of microspheres and microcapsules has been long-acting injectable drug depot formulations with specific drug targeting and delivery optimization [37]. These systems have been under evaluation for ophthalmic drug delivery purposes during the past 20 years. Among the biodegradable polymers that have been investigated to make microparticles for drug delivery are gelatin, albumin, polyorthoesters, polyanhydrides and polyesters, particularly polymers of D-, L- and DL-lactic acid (also known as poly(lactic acid), polylactide, or PLA) and poly-(glycolic acid) (poly(glicolide), PGA), and copolymers of lactic and glycolic acids (also known as poly(lactic-*co*-glycolic)acid, poly(lactide-*co*-glycolide) and PLGA). These polyesters have been used most frequently to make microspheres for subconjunctival and intravitreal drug delivery. Among the polymeric particles potentially useful for ocular drug delivery, the microspheres have been used most often [37]. **Figure 1** demonstrates scanning electronic microscopy images of ciprofloxacin-loaded PLGA microspheres utilized in most of the authors' studies.

Subconjunctival ocular drug delivery represents another attempt to elevate intraocular drug concentrations and

minimize the frequency of dosing [33]. Compared with direct intraocular injection, this approach is less risky to the patient and less invasive. As sclera is much more permeable than conjunctiva, the formidable permeability barrier consisting of both cornea and conjunctiva can be avoided altogether in such approaches [38,39]. The advantage of subconjunctival implants as opposed to conjunctival injection of solution is the achievement of higher drug concentrations and sustained release of the drug in both aqueous and vitreous humors and even retinal areas [33]. DL-Polylactide (PLA) nano- and microparticles containing budesonide (which inhibits the expression of VEGF for the treatment of angiogenesis in the retina) are reported to afford sustained release of budesomide *in vitro*. Subconjunctival injection of PLA microparticles (3.6 μm) led to a much higher budesonide concentration in retina and vitreous humor over 14 days, compared with the solution form of dosing and PLA nanoparticle (345 nm) administration [31]. Gilbert and co-workers demonstrated that collagen matrix and fibrin sealant, compared with a conventional solution form of dosing, provided a better controlled release of cisplatin and carboplatin, respectively, attaining higher drug concentrations after subconjunctival administration in rabbits in several ocular tissues, including retina [32,40].

Transscleral delivery is a minimally invasive method that achieves targeted delivery of higher therapeutic levels of anti-infective and anti-inflammatory drugs to the anterior and posterior segments of the eye. This drug delivery modality shows linear kinetics of absorption and elimination, with the potential to deliver constant doses of medication. By bridging the potential late-generation antimicrobials to the need for focused and engineered pharmacologic intervention, transscleral delivery of biodegradable microparticles sits at the crossroad of patient comfort, treatment compliance and enhanced protection.

2.2 Postoperative ocular inflammation
In the modern cataract surgery era, although inflammation is minimal, a more comprehensive medical management
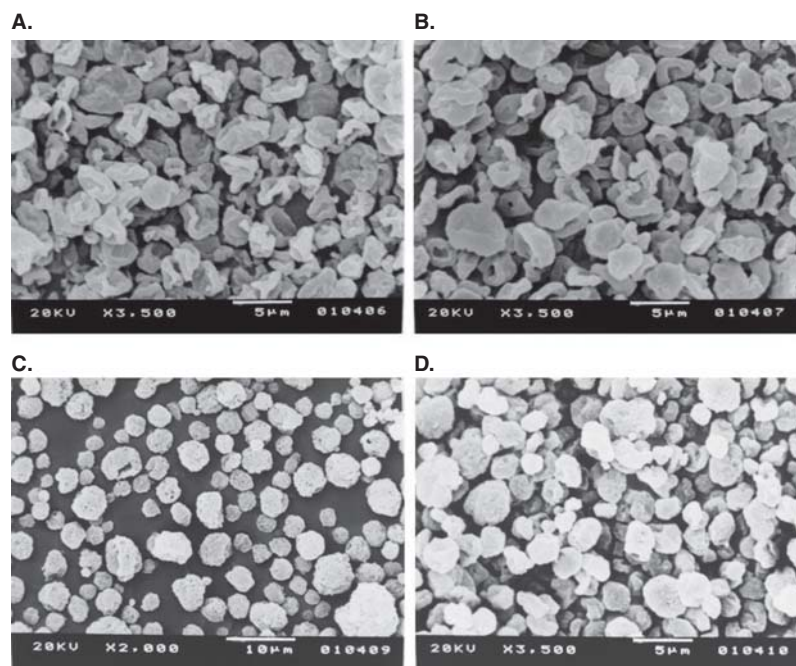
Figure 1. Scanning electron microscopy images of ciprofloxacin-loaded PLGA microspheres with drug/polymer proportions of (A) 1:1, (B) 1:2, (C) 1:3 and (D) 1:5 (w/w).

strategy to treat such inflammation is still to be determined. Historically, corticosteroids have been the drugs of choice for the prevention of postoperative ocular inflammation and are commonly used for several weeks. Ozurdex™ (Allergan, Inc, Irvine, California), an intraocular sustained release pellet of dexamethasone implanted at the anterior chamber at the end of the surgical procedure, has proved to be effective in eliminating the necessity for postoperative topical therapy, at the cost of potential movement and displacement of the implant as the main side effects [4-6]. In addition, there is not sufficient literature evidence to support its routine clinical acceptance. The sustained anti-inflammatory effects associated with the use of triamcinolone in the ophthalmic setting have prompted the authors to consider its therapeutic use for controlling post-cataract surgery inflammation. A sub-Tenon's capsule depot corticosteroid injection may satisfy all the requirements for an ideal anti-inflammatory strategy and may have distinct advantages for reducing complications related to patient non-compliance with eye drop administration.

The authors' recently published study comparing a single intraoperative sub-Tenon's capsule injection of triamcinolone with conventional prednisolone eye drops substantiates a new and more comprehensive anti-inflammatory strategy for cataract surgery [17]. Consistent with previous investigations [17,18], the results indicated that one 25-mg sub-Tenon's capsule triamcinolone acetonide injection resulted in a therapeutic response and ocular tolerance comparable to 1% prednisolone acetate drops in controlling the signs and symptoms of ocular

inflammation after cataract surgery. On the first postoperative day, all patients in both groups had anterior chamber cell and flare scores that gradually decreased over time. The parallel decreases in both groups suggested that triamcinolone is at least as effective as conventional prednisolone eye drops in reducing postoperative inflammation. As a result, a sub-Tenon's capsule injection of depot corticosteroid, an already accepted method for the treatment of various inflammatory ocular diseases, could be useful in the surgical arena. It provides a new way to eliminate patients' self-medicating, avoiding problems with compliance and instruction. Furthermore, when this demonstration of the anti-inflammatory effects is coupled with its ability to treat cystoid macular edema and diabetic macular edema aggravated by the surgical intervention [11-16,18,41], a clear role for triamcinolone as a simple and more rational management strategy for post-cataract surgical inflammation begins to emerge.

One posterior sub-Tenon's capsule triamcinolone injection also had ocular tolerance equivalent to prednisolone eye drops through 4 weeks of follow-up. There were no significant differences between the two treatment groups in the number of adverse events, changes in visual acuity, or lack of response [17]. The potential complications of sub-Tenon's capsule injection of corticosteroids include inadvertent injection into the choroidal or retinal circulation [42-44], globe perforation [45-47] and occlusion of the central retinal artery [48]. Blepharoptosis, proptosis, orbital fat atrophy, delayed hypersensitivity reactions, strabismus, conjunctival hemorrhage, chemosis and infection also have been reported [49-52].

An increase in intraocular pressure (IOP) after topical or systemic administration of corticosteroids is of particular concern [53]. Patients who receive sub-Tenon's capsule injections of corticosteroids may not respond to maximal anti-glaucomatous therapy and, therefore, may require surgical excision of the depot because of a persistently elevated IOP [54]. As increased IOP may be a function of the interaction between the disease itself and the use of topical or systemic corticosteroids, the role of posterior sub-Tenon's capsule corticosteroids in ocular hypertension is not always clear; therefore, these concerns may not apply to patients who underwent surgery whose status in responding to corticosteroids is unknown. Following a posterior 40-mg triamcinolone sub-Tenon's capsule injection, a surprisingly lower than expected incidence of increased IOP was observed [17]. In the authors' most recently study, only one eye (triamcinolone group) had an IOP that exceeded 25 mmHg, and the IOP returned to a normal level with topical antihypertensive drops [34]. However, beyond the 28-day follow-up period, delayed onset of increased IOP must be considered. The depot formulation was placed forward under sub-Tenon's capsule and, if an intractable IOP increase occurred, the remainder of the depot could easily be removed.

Other authors have also confirmed the theory and similar results have been published applying a similar technique argeting cataract and retina surgery [18,55]. Although definitive conclusions cannot be drawn based on these initial findings, the results support further investigation [17]. A large Phase III multi-center trial is being considered to evaluate this potential treatment. Investigation of the latest-generation fluoroquinolone formulation combined with non-steroidal anti-inflammatory drugs is now underway in the authors' laboratory and will be the next level of improvement for this suggested system.

In summary, the suggested anti-inflammatory approach may provide the ophthalmologist with an alternative tool to costly controlled drug delivery and eliminates the need for patient self-medication, which avoids problems with compliance and instruction. Such an approach could be especially important in the Third World, where topical medications may not be available after intraocular surgery.

3. Anti-infective prophylaxis for cataract surgery

3.1 The importance of high drug concentration
The achievement of high antimicrobial concentrations within infected tissue is important for several reasons. First of all, for the therapy to be effective the necessary bactericidal concentrations to eradicate the pathogen must be achieved and maintained. The bactericidal activity of fluoroquinolones is largely concentration dependent, which explains why peak concentration values and the 24-h AUC to minimum inhibitory concentration MIC(90) are important determinants of individual drug activity (potency). Higher drug exposure and total dosages, as indicated by higher AUCs, may be associated with more effective eradication of the infecting organism [56]. Second, the emergence of bacterial resistance to fluoroquinolones also appears to be concentration dependent [57-59]. At fluoroquinolone concentrations above the MIC, the frequency of pathogen mutation increases exponentially as the concentration decreases. This means that the use of fluoroquinolones that can result in tissue concentrations only modestly above the MIC could result in the development of antimicrobial resistance to that fluoroquinolone [59]. Thus, the ability of a drug to produce high drug concentrations within infected tissues may facilitate enhanced antibacterial activity with a reduced likelihood of emergence of resistance. For a future and revolutionizing therapy, this required target could be achieved only by the development of an eye-specific antimicrobial agent or by an appropriate drug delivery approach engineered to enhance drug penetration [60].

3.2 Conventional antibacterial strategy and its shortcomings
The route for local ophthalmic drug delivery remains the topical application of solutions at the surface of the eye as drops. Drug delivery to intraocular tissues by this approach, however, is limited by: (i) the significant barrier to solute flux provided by the corneal epithelium; and (ii) the precorneal drug loss that occurs by way of the tear fluid turnover. Despite the relatively small proportion of a topically applied drug dose that ultimately reaches intraocular tissues, topical formulations can achieve therapeutic concentrations in anterior segment tissues, largely because of the very high concentrations of drugs that are administered. It has been estimated that typically < 5% of a topically applied drug actually permeates the cornea and eventually reaches intraocular tissues. The major portion of the instilled dose is absorbed systemically by way of the conjunctiva, through the highly vascular conjunctival stroma and through the lid margin vessels. Systemic absorption also occurs when the solution enters the nasolacrimal duct and is absorbed by the nasal and nasopharyngeal mucosa [24,61].

Conventional ocular pharmacokinetics has downplayed the possibility of any high effective transfer of a drug from an eye drop to the aqueous and vitreous humors [27]. Widely accepted for conjunctival and corneal infection, new antimicrobial drops are often exploited for prophylaxis use for intraocular infections without rationalizing the penetration characteristics. However, despite the physiological processes involved in guarding the eye against xenobiotics, the newer fluoroquinolones have demonstrated excellent ocular penetration after topical administration, using an extremely high loading dose [62,63]. A careful literature and methods review will point to an unacceptably high antimicrobial loading dose and single point measurement (usually at a short- and higher peak concentration-time point) attempting to demonstrate the potential of the newer-generation fluoroquinolones to

overcome the highlighted delivery barriers. Tested in a practical clinical setting where a single drop is instilled every 4 – 6 h with poor patient compliance, even late-generation antimicrobials may face obstacles in reaching high, but more importantly, sustained therapeutic levels. In support of the authors' theory against topical antimicrobial delivery in cataract surgery, their laboratory has elaborated a more simplistic and realistic investigational method to address experimentally the role of topical prophylaxis in the surgical scenario.

An aqueous humor bioactivity comparison of several fluoroquinolones following a single topical drop delivery was carried out in the authors' laboratory with the single purpose of evaluating quantitatively over time the bioactivity of ciprofloxacin 0.3%, levofloxacin 1.5%, gatifloxacin 0.3% and moxifloxacin 0.5% in aqueous humor of rabbit eyes. For supportive methods, a total of 64 New Zealand rabbit eyes were topically treated with a commercially available formulation of ciprofloxacin 0.3%, levofloxacin 1.5%, gatifloxacin 0.3% and moxifloxacin 0.5% eye drops. Following an initial loading dose consistent of a single antimicrobial drop the aqueous humor was sampled at 30 min, and 1, 2 and 4 h posttreatment. Biological activity was indirectly determined from the size of the zone of inhibition (ZOI) of a filter paper disc soaked in 25 µl of aqueous humor withdrawn from treated eyes and placed on an agar plate surface cultured with *Staphylococcus epidermidis.* Moxifloxacin eye drops (0.5%) showed an initial (30 min and 1 h post-treatment) trend towards superior aqueous bioactivity compared with all other tested formulations (**Figure 2**). At the second and following hour, the aqueous humor withdrawn from all treated eyes failed to demonstrate any bacteria inhibitory potential for the four tested formulations, as no zone of inhibition could be observed. The main conclusion of this complementary method in antimicrobial bioactivity exploration is that sole reliance on the minimum inhibitory concentration and artificial pharmacokinetics studies as a guide to antibacterial efficacy may be misleading, and even newer-generation fluoroquinolones failed to demonstrate a significant aqueous bioactivity using a dosing regimen that simulated prophylactic use after cataract surgery.

As a result, despite surrogate studies showing that topical antimicrobials decrease bacteria on the ocular surface and anterior chamber, and that some topical antimicrobials can penetrate the cornea and the anterior chamber [62-65], there has not been a prospective randomized study showing that topical antimicrobials prevent endophthalmitis. Bioavailability has been touted in the literature, but its relationship to endophthalmitis in humans is unknown. In one rabbit study, several drops of moxifloxacin preoperatively prevented endophthalmitis from developing [66]; this was the first study to suggest that topical antimicrobials alone can prevent endophthalmitis. Once an organism reaches the vitreous humor, however, topical application of antimicrobials is probably not efficacious [67]. Furthermore, *in vitro* susceptibility data and animal studies cannot be translated uniformly into

*in vivo* efficacy because of further factors, such as anatomic location and pharmacodynamics.

3.3 Uncertainty in alternative methods of endophthalmitis prophylaxis

Almost all surgical specialties, except ophthalmology, have published joint guidelines for antimicrobial prophylaxis of postsurgical infection [68]. With only limited evidence-based information available, ophthalmologists use surrogate studies and/or personal experience. Studies confirm that the organisms detected in endophthalmitis are frequently present in the preoperative periocular flora [69], that organisms may stick to intraocular lens (IOL) during surgical placement and form biofilms [70], that organisms enter the anterior chamber during surgery, and that organisms enter the anterior chamber in the postoperative period [71], especially in this era of clear cornea incision [72]. The duration of high antimicrobial levels in the anterior chamber after intracameral administration is short, whereas the risk for contamination through unsealed clear cornea wounds last for many days. In addition, intracameral antimicrobials do not address the significant risk of contamination from the surface of the eye, which remains until the surgical incision heals. In a study by Moshifar *et al.* [73], the time to presentation of endophthalmitis averaged 9.6 days postoperatively, exceeding 7-day administration of postoperative topical antimicrobials, and certainly beyond the time frame of an intracameral antimicrobial. Alternative antimicrobials as well as antimicrobials approved for topical use only have also been suggested for intracameral use, although they have not been sufficiently evaluated.

Possible modes of antimicrobial administration include topical antimicrobials, subconjunctival injections, infusion fluid antimicrobial placement, intracameral bolus injection, soaked implants, oral administration and transcorneal iontophoresis [74-76]. Several modest studies support subconjunctival antimicrobials, with a lack of studies refuting these findings. There are no large randomized controlled prospective clinical trials evaluating the ability of antimicrobials in the irrigating solution to lower significantly the incidence of endophthalmitis, although various rigorous studies suggest a benefit. Compared with topical administration, intracameral antimicrobial injection has the advantage of providing a much higher intraocular concentration. However, there is interest in exploring other methods of antimicrobial delivery that could enhance and prolong the maintenance of effective intraocular antimicrobial concentrations after cataract surgery. Overall, a multipronged approach to limit endophthalmitis is needed, with antimicrobials as only part of the strategy.

4. Subconjunctival delivery of antimicrobials in a controlled release microsphere system

To the best of the authors' knowledge, their recently published investigations open up a new era of no postoperative drops for cataract surgery [17,34,35]. These studies disclosed
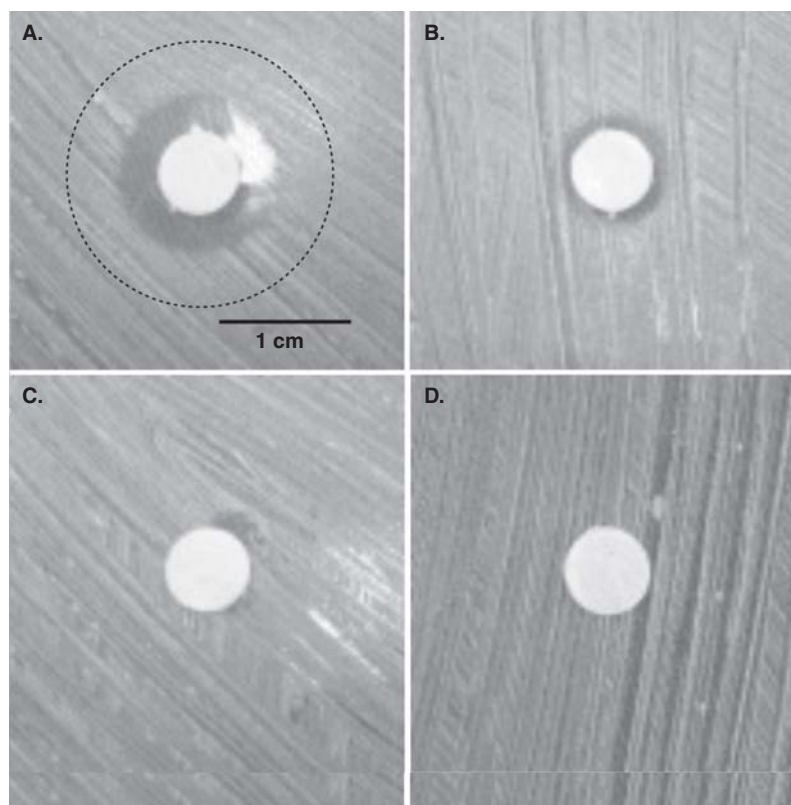
Figure 2. Aqueous humor bioactivity following the delivery of a single topical drop of moxifloxacin 0.5% evaluated quantitatively over time: (A) 30 min, (B) 1 h, (C) 2 h and (D) 4 h post drop instillation. Biological activity was indirectly determined from the size of the ZOI of filter paper disc soaked in 25 μl of aqueous humor withdrawn from treated eyes and placed on an agar plate surface cultured with *Staphylococcus epidermidis.* Although not significant (all ZOI measurements were below the minimum size expected for an efficacious therapeutic response), 0.5% moxifloxacin eye drops showed an initial (30 min and 1 h post-treatment) trend towards superior aqueous bioactivity compared with all other tested formulations (dotted circle: moxifloxacin minimum expected ZOI for the studied *S. epidermidis* = 20 mm). For all the other antimicrobials tested (ciprofloxacin 0.3%, levofloxacin 1.5%, gatifloxacin 0.3%), no ZOI could be observed (not shown).
ZOI: Zone of inhibition.

pioneering information and substantiated a new and optimized antimicrobial prophylaxis strategy using slow-delivery technology. Superior vitreous penetration and immediately higher concentrations of antimicrobial in the aqueous humor, when compared with the common practice of dosing eye drops six times daily, support and add rationale to the use of a slow-release transscleral drug delivery system in preventing endophthalmitis after cataract surgery. In addition, when this pharmacologic achievement is coupled with its ability to free the patient of the nuisance of topical administration, a clear role for this system as a simple and more comprehensive weapon for fighting postoperative infections begins to emerge.

By exploring superior sclera permeability and to avoid the rate-limiting barriers of the cornea and conjunctiva, subconjunctival routes may offer a promising alternative for enhanced drug delivery and tissue targeting compared with topical routes [22-27]. Confirming the authors' premise, the controlled release microsphere delivered therapeutic concentrations of antimicrobial greater than the minimum inhibitory concentration for most common ocular pathogens up to 10 days after injection. The dosing regimen tested in this experimental investigation fits into a realistic clinical scenario and may provide a surrogate to assess achievable postoperative concentrations. Similar to previous studies [31-33], the parallel and higher aqueous and vitreous levels of ciprofloxacin-loaded microspheres, as opposed to the same concentration of ciprofloxacin in its free form after a single subconjunctival injection and to topical ciprofloxacin delivery, are considered a highly desirable pharmacological achievement. Furthermore, given the inherent advantages of intraoperative sustained release antimicrobials, particularly regarding patient compliance and convenience, the studied system may achieve a breakthrough in the development of more successful treatment modalities, suggesting a possible new way to progress anti-infective prophylaxis in parallel with antimicrobial drug development.

In an experimental rabbit model of endophthalmitis prophylaxis, the 'proof of principle' has been demonstrated that prophylaxis with a biodegradable controlled release system delivered transscleral through a single subconjunctival injection can reach sustained therapeutic levels in the anterior chamber that predictably reduced bacterial recovery and signs of clinical endophthalmitis (comparable to conventional topical drops). Extrapolating these findings to clinical settings, where typically patients are non-compliant to treatment, a potential superior performance of a microsphere system over conventional postoperative drops could be postulated and expected. The frequency of application is important for attaining adequate antibacterial concentrations, and poor compliance also prevents the drops from reaching efficacious levels. Compliance with topical therapy was studied using an electronic device in ambulatory patients who underwent cataract surgery; all patients were non-compliant regarding total dose, time intervals and premature discontinuation of therapy [77].

As an adverse event is an important concern with any new dosage form, it is also important to ensure that the system chosen for cataract prophylaxis is safe and well tolerated, eliminating any potential toxicity. The biocompatibility of periocular microspheres of biodegradable polymers has been investigated extensively. *In vivo,* no drug or procedure-related adverse events occurred and no inflammatory cells or fibrous tissue response were observed at the site of injection. Clinically, in addition to its minimally invasive and cosmetically acceptable nature, no drug or procedure-related adverse events occurred [34-35].

In conclusion, the scientific observations suggest that both topical drops and microsphere injection may be equally tolerated and effective. The antimicrobial delivery system helped to eliminate non-compliance issues. By freeing the patient from the nuisance and expense of topical therapeutic, a new anti-inflammatory and anti-infective paradigm in the modern cataract surgery arena has been introduced and merits further consideration. In parallel to antimicrobial development, exploiting the routes for transscleral delivery or circumventing the cornea–conjunctival barriers will be the key to an ultimate anti-infective strategy in the modern cataract surgery era. Although the challenges are formidable, the experimentally and clinically tested system holds promise for new paradigms in dosing anterior segment drugs.

5. Expert opinion

5.1 Optimal anti-inflammatory control for the new era of cataract surgery
Lack of commercial viability and an extremely high budget to fund prospective randomized clinical trials translate into attenuated enthusiasm among pharmaceutical companies in search of innovative and advanced therapeutic strategy. In several technological and safety aspects the cataract surgery technique has improved significantly over the past two decades. Postsurgical inflammation is now minimal. However, physicians still rely on an obsolete, perhaps inadequate or at least non-optimized, method of drug delivery for this modern era. A sub-Tenon's capsule depot corticosteroid injection may satisfy all the requirements for an ideal anti-inflammatory strategy and may have distinct advantages for reducing obstacles related to patient non-compliance and comfort with eye drop administration. Furthermore, when this anti-inflammatory effect is coupled with its ability to treat concomitantly cystoid macular edema and diabetic macular edema aggravated by cataract surgery [11-16,18,35], a clear role for triamcinolone as a simple and more rational management strategy for post-cataract surgical inflammation begins to emerge.

5.2 Antibiotic prophylaxis in cataract surgery and the urgent need for an eye-specific antibacterial agent and delivery optimization
A principle of prophylaxis is that the antimicrobial need not sterilize the tissue, but its function is to decrease the load so the body (e.g., anterior chamber) can handle any residual [78]. Many extend the role of topical antimicrobial into clearing the anterior chamber and saturating the cornea, but clinical efficacy in humans is not available and there does not seem to be enough robust data to support the superiority of latest-generation antimicrobials. In fact, most infectious disease experts prefer to reserve the potent antimicrobials for the treatment and use lesser antimicrobials for prophylaxis.

Regarding the proper antimicrobial delivery route, despite its 'off label' nature, with no strong scientific evidence supporting its preventive value, topical antimicrobial therapy remains the standard of care in postoperative endophthalmitis prophylaxis among cataract surgeons. Earlier retrospective studies and case series suggest adjunctive intracameral antimicrobials may reduce further the incidence of postoperative endophthalmitis in patients having cataract surgery. Compared with topical administration, intracameral antimicrobial injection has the advantage of providing a much higher intraocular concentration. However, there is an interest in exploring other methods of antimicrobial delivery that could enhance and prolong the duration of maintenance of effective intraocular antimicrobial concentrations after cataract surgery. The ideal agent should offer potent activity against the common pathogens, favorable surface, intracameral and intravitreal pharmacokinetics, minimum potential to promote resistance, excellent safety, and ease of use. When judged against these criteria, intracameral and topical delivery have several shortcomings. On the other hand, transscleral delivery is a minimally invasive method that achieves targeted delivery of higher therapeutic levels of anti-infective and anti-inflammatory drugs to the anterior and posterior segments of the eye. Furthermore, given the inherent advantages of intraoperative sustained release antimicrobials, particularly regarding patient compliance and convenience, this technology may achieve a breakthrough

in the development of more successful treatment modalities, suggesting a possible new way to progress anti-infective prophylaxis in parallel with antimicrobial drug development. By bridging the potential of late-generation antimicrobials to the need for focused and engineered pharmacologic intervention in cataract surgery, transscleral delivery of biodegradable microparticles sits at the crossroads of patient comfort, treatment compliance and enhanced protection. However, no study will provide the final answer regarding optimal antimicrobial prophylaxis. Advances in antimicrobial

therapy and modes of delivery will make prophylaxis for ocular infection and modes of drug delivery a dynamic area and will highlight the need for continuing investigation and periodic review of guidelines to maintain pace with new developments in optimizing patient care.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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