Expert Opinion

Intraocular penetration of antimicrobial agents in ophthalmic infections and drug delivery strategies

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Conventionally, antimicrobial drugs developed and approved for systemic infections are re-investigated for ocular infections. However, developing a new antimicrobial agent with good intraocular penetration by considering the anatomical and physiological constraints exerted by the barriers of eye is not a popularly perceived strategy. For the last three to four decades much emphasis has been placed on drug delivery systems to enhance the ocular penetration of antimicrobial agents. In order to compare ocular drug delivery strategies for ocular infections, the existing studies and methods were revisited using an extensive literature search. The present analysis also encompasses the scientific outcomes of endophthalmitis studies to interpret the intraocular penetration data of various antimicrobial agents and their requirements before and after the onset of inflammation. This article critically analyses the systemic and topical drug delivery methods adopted for antimicrobial use and their applicability to the newer class of antimicrobial agents, thus giving space for further developments. This review emphasizes the requirement of stage-by-stage insights about ocular infections, the need for an eye-specific antimicrobial agent and the inevitability of an appropriate drug delivery approach to revolutionize future therapy.

Keywords: Antibiotics, antimicrobials, bacterial keratitis, endophthalmitis, eye drops, eye infections, intraocular penetration, ocular drug delivery

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1. Introduction

Topical medication for ocular therapy has been known to mankind for centuries. Ancient civilizations like Mesopotamia and Indian *Vedic* records bear evidence to this fact. Topical forms of therapy have been rationalized by considering the eye as an isolated entity which needs a local mode of drug application. Despite the multidimensional drug development approaches of the contemporary period, it is rare to see any specific antimicrobial agent being developed for ocular use considering the penetration constraints exerted by the eye after topical or systemic administration. Therefore, drugs for systemic use are often exploited for ocular use without rationalizing the penetration characteristics in the drug development stage. Lack of commercial viability in concert with an absence of clarity or consensus about the underlying mechanisms of drug penetration into the eye translates into attenuated enthusiasm among pharmaceutical researchers. This hinders the exploration of novel therapeutic approaches for the eye with appropriate newer molecules.

Therefore, the onus of ophthalmic antimicrobial drug development rests on drug delivery systems to enhance penetration, rather than their molecular penetration

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properties. The strategies employed for the delivery of antimicrobial agents are shown in **Figure 1**. Ocular drug penetration is complicated by the physiological processes involved in guarding the eye against xenobiotics. The presence of blood ocular barriers at the three main ports of drug entry to the eye, namely the topical, aqueous and retinal routes, determines the intraocular concentration of antimicrobial agents into the humors of the eye. Due to these barriers, reaching and sustaining an adequate concentration of antimicrobial substances above MIC_{90} of the invading microbe becomes a formidable task in the treatment of ocular infections with bacterial, fungal or viral origins.

There are two major issues to consider when dealing with ocular penetration of antimicrobial agents: one is prophylactic drug administration to reduce the possible risk of infection after surgical manipulations. In this condition, the drug is expected to penetrate the non-inflamed eye. The second is chemotherapy to the inflamed eye as a result of infection in the ocular structures. These two conditions can very well be appropriated with non-inflamed and inflamed conditions of the eye respectively, with some exceptions.

1.1 Scientific gains from endophthalmitis studies

Post-operative endophthalmitis in cataract surgery is the most common presentation in many ophthalmic clinics and indeed one of the most fearsome complications of cataract surgery. The conclusions from the Endophthalmitis Vitrectomy Study (EVS) remain as the basis for the management of post-cataract surgery endophthalmitis, notably prompt intravitreal antibiotic administration after vitreous sampling, with consideration for pars plana vitrectomy in severe cases [1]. The results of European Society of Cataract and Refractive Surgeons Study (ESCRS study) showed that the group that utilized cefuroxime injection in the anterior chamber upon completion of the cataract surgery achieved a significant reduction of the prevalence of endophthalmitis. Whereas the use of levofloxacin eye drops immediately after the operation failed to achieve a statistically significant reduction of the frequency and risk of endophthalmitis after cataract surgery [2]. A risk factor analysis study for infectious endophthalmitis complicating cataract surgery in the UK reported that subconjunctival antibiotics at the end of surgery affords significant protection against post-operative infection [3]. Furthermore, a retrospective evaluation revealed that pars plana vitrectomy followed by intravitreal amphotericin B and dexamethasone with or without oral fluconazole or itraconazole showed a successful outcome in the clinical management of fungal endophthalmitis [4].

1.2 Antimicrobial penetration in non-inflamed and inflamed eyes

The crux of the EVS, ESCRS and other studies addressing the management of post-operative endophthalmitis supports a general hypothesis that poor or no intraocular bioavailability of antimicrobial agents and the absence of first line immune defense inside the vitreous contribute to the unrestricted growth of microbes in the initial phase when the barrier permeation of drugs is not increased.

When the microbe level reaches a critical mass in its log phase, the barrier is broken by the bacteria/bacterial metabolites causing inflammation leading to increased vitreous drug concentration. At this stage drug concentration in the vitreous may not be adequate to give antimicrobial protection. This could be the reason for the ineffectiveness of systemic antibiotics in the inflamed eyes. Even though the penetration in inflamed eyes increases far beyond than that of normal penetration, there is no special enrichment step to increase vitreous concentration beyond plasma levels. Therefore, in most of the trials, decreasing the microbial load by partial vitrectomy is found to be of practical advantage, along with direct intravitreal injection of higher antimicrobial dosage. The failure of systemically given antimicrobial agents in endophthalmitis was well documented in the EVS study.

1.3 Conventional antimicrobial strategies and their shortcomings

From all the sites, ocular humors are protected by barriers. Anterior entry of xenobiotics through the cornea is blocked by an efficient bio-membrane 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 less than 5% of the applied dosage. One of the key factors affecting corneal penetration of the drugs is the degree of ionization of the drug in the tear film pH. Non-specific irritation caused by the drug on the corneal nerves stimulates reflux tear flow, which substantially decreases corneal penetration. The volume of the eye drop (low volume having better bioavailability) and formulation factors (irritant preservatives, osmolarity, viscosity, bioadhesive nature, pH, etc) are other indicators that govern the intraocular penetration of topically applied drugs. *In vitro* corneal penetration of drugs have been employed in many earlier studies and based on these data, assumptions were drawn about the drug penetration characteristics. As far as topical drug penetration is concerned, without considering the drug ionization in the tear film and continuous washout model, predicting the exact intraocular penetration is not possible. Evidence suggests that attempts to achieve adequate drug penetration into the eye through systemic administration of antimicrobials have also suffered due to blood, retinal and aqueous barriers. Although ocular-specific drugs were not given importance in the past, various formulational approaches have recently been attempted to circumvent their shortcomings. Therefore, this review focuses on results from past and recent studies documented in the literature to rationalize the prominent individual approaches attempting to increase antimicrobial penetration across the cornea and ocular barriers.

Table 1. Drug delivery systems adopted for the injectable use of antimicrobial drugs: their advantages and limiting factors.

Type of delivery	Advantages	Limiting factors for widespread use
Intravenous infusion	Easy and conventional way to infuse and maintain steady state levels	Poor intraocular availability in non-inflamed eye
Intravitreal injection	Increases very high levels directly into the site of action (vitreous cavity)	Fast elimination (still reliable and only option available as of now). Drug elimination is faster in non-inflamed eyes
Liposome or nanoparticle or solid lipid nanoparticles	Extended the intraocular residence time of the drug	Efficiency not proved well
Intracameral injection	Directly increases drug concentration in the aqueous humor	Studied in patients undergoing cataract surgery and limited studies on other cases
Subconjunctival injection	Increases the drug concentration in cornea and aqueous humor	Invasive technique
Altering drug transporters	Blocking the barriers theoretically expected to increase the ocular penetration	Presently under evaluation; few studies are available. Safety is a concern
Minipump	Delivering and sustaining the levels are possible	Complicated set-up not studied in humans
Drug releasing intraocular lenses	Rationale to release drug after IOL implantation for first 12 hours	Limited to cataract surgery and more controlled studies required
Sustained release inserts	Suitable for prolonged sustained release into the vitreous cavity	Limited by certain surgical complications

2. Injectables and other deliveries for intraocular infections

2.1 Systemic route of drug administration

2.1.1 Oral drug therapy

Several investigations have documented the intraocular penetration of orally administered drugs. The intraocular bioavailability is highly relevant to plasma concentration achieved after its absorption from the intestine. The extent of antimicrobial drug absorption and resulting plasma concentration is governed by the physiochemical and pharmacokinetic property of the drug. Its distribution into the eye is based upon its physiochemical (may be different from intestinal absorption) and transporter susceptibility to ocular barriers. Even newer fluoroquinolones showed inadequate intraocular penetration in non-inflamed eyes, which includes moxifloxacin [5], gatifloxacin [6], ciprofloxacin [7] and ofloxacin, sparfloxacin and lomefloxacin [8]. Thus using them as a monotherapy for prophylaxis was cautioned against. Therefore, reaching antimicrobial concentrations (above MIC_{90} of all ocular pathogens) of drugs into the vitreous as a prophylactic measure remains uncertain with the available class of antimicrobial agents.

2.1.2 Intravenous injection

The i.v. route is favored in order to achieve a higher site concentration for systemic infections. But this approach has limited application in case of prophylactic treatment for ocular infections. Intraocular oxacillin penetration was compared between a continuous i.v. infusion and subconjunctival injection, or combined therapy in a rabbit model of *Staphylococcus aureus* endophthalmitis [9]. This study showed that under the equilibrium conditions achieved by i.v. infusion, concentrations in the aqueous humor, cornea and choroid-retina were 25 – 30% of the serum levels, whereas vitreous reached only 2% of the serum concentration. Subconjunctival injection produced extremely high levels in the cornea and aqueous and moderate concentrations in the choroid-retina, whereas vitreous penetration remained poor (< 1 µg/ml). These data suggest that reaching more than 50 µg/ml as serum level resulted in vitreous levels greater than 0.4 µg/ml. Therefore, this study first recommended indirect intravitreal injection of antibiotic rather than the i.v. route. The percentage of oxacillin penetration under the equilibrium conditions of this study showed 0.8% penetration into the vitreous.

To determine the delivery of systemically administered cefazolin to the vitreous cavity of traumatized and non-traumatized eyes, Nossov *et al.* [10] used the pig model of penetrating ocular trauma. Three 8-hourly doses of 36, 79 and 190 mg/kg and nine 8-hourly doses of 17 mg/kg were administered and vitreous levels were assessed. In this study 190 mg/kg dosage reached a serum concentration of 49.3 µg/ml, resulting in vitreous levels of 15.6 µg/ml in only the traumatic eye; whereas the control eye showed levels less than 1 µg/ml. All other doses failed to reach levels more than 1 µg in both the groups [10]. Intravenously infused imepenem 1 gm is reported to reach vitreous levels of 2 µg/ml at 2 hrs in non-inflamed human eyes, which is reported to be above the MIC_{90} of main bacterial species

Table 2. Drug delivery systems adopted for the topical use of antimicrobial drugs: their advantages and limiting factors.

Type of delivery	Advantages	Limitations
Eye drops with viscosity enhancers or mucoadhesive polymers	Good patient compliance, cost effective, increases pre-corneal retention time, gives additional boost to intraocular penetration	Not able to increase the penetration exceeding MIC_{90} of all microbes
Ointments	Conventional technique, cost effective and reported to reach higher levels of drug in the cornea	Daytime application is restricted and gives sticky sensation and co- administration of other eye drops are not possible
Liposomes and nanoparticles	Increases the intraocular penetration	Low stability and single dose reconstitution and instillation is not a convenient task for the patient
Drug-soaked contact lenses	Extensively studied and reported to decrease the precorneal drug clearance	Studies showed fortified eye drops are equivalent to drug-soaked contact lenses
Soluble ophthalmic delivery inserts	Releases slowly upon degradation, sustains precorneal and enhances intraocular penetration	Recent studies with fluoroquinolones shows no advantage.
Iontophoresis	Increases intraocular permeation, non-invasive	Fear of corneal scleral burn, several patents on the design restricting its commercial use
Therapeutic wicks	Studied from one centre and used for a long time. Mass application made easy	Technical information about standardization, controlled studies and rationale are not available
Transporters	More rationalized approach	Usage of appropriate blockers and extent at which a particular transporters contribution are not clear. Safety needs to be established

responsible for endophthalmitis [11]. A single dose of 2 gm meropenem showed aqueous levels of 13.4 and 1.1 μg/ml and vitreous levels of 8.9 and 1.1 μg/ml at 30 min and 12 hr respectively. The above-mentioned levels were reported to be above MIC_{90} of ocular pathogens. Even though β-lactam carbapenems like imepenem and merapenem were reported to show concentration in the vitreous above MIC_{90}, further studies are required to critically evaluate its suitability in endophthalmitis. A comprehensive review by Robert and Tassy regarding ocular bio-availability of other antibiotics after i.v. injection offers further information regarding the same [12].

2.2 Intracameral injection

Following the i.v. route, the intracameral injection of antimicrobial agents generated much interest among ophthalmologists as an effective method of achieving optimum therapeutic concentrations in the anterior segment. Three patients of culture proven *Aspergillus flavus* corneal ulcer with hypopyon not responding to topical natamycin (5%), amphotericin B (0.15%) or oral itraconazole responded to intracameral amphotericin B without any corneal or lenticular toxicity [13]. The ESCRS-sponsored study for post-operative endophthalmitis prophylaxis reported that the rates of presumed infectious post-operative endophthalmitis is much less (0.07%) with intracameral cefuroxime treatment as compared to the control group (0.34%) [14]. Even though ESCRS trial investigators and other ophthalmic surgeons favored the commercial availability of fourth generation fluoroquinolones, controlled animal studies are not available to rationalize the intracameral pharmacokinetics of these antimicrobial agents.

2.3 Subconjunctival injection

Subconjunctival injection has been reported to be a successful route to reach higher antimicrobial concentration in the anterior segment of the eye. Subconjunctivally, a given antibiotic was reported to penetrate the eye by direct diffusion [15]. Subconjunctival injection of acyclovir was reported to reach higher drug levels in both the cornea and aqueous humor as compared to 3% topical ointment [16]. The highest drug concentrations in the cornea after subconjunctival injection were reached adjacent to the injection site and levels were reported to decrease as the distance from the injection site increased [17]. However, toxic reactions of the surrounding structures due to this mode of injection was also reported [18]. Furthermore, subconjunctivally given antibiotics such as vancomycin, ceftriaxone and ceftazidime reached exceedingly low levels in the non-inflamed vitreous in humans [19]. Therefore, giving antimicrobial protection in the vitreous by the subconjunctival route is compromised due to the low drug penetration into the posterior segment. A recent retrospective study compared intracameral with subconjunctival cefuroxime injected at the end of cataract surgery. This study reported that intracameral cefuroxime

showed a significant reduction of post-operative endophthalmitis and was a safe alternative to subconjunctival injection [20,21]. In the present scenario most of the studies suggest and practice more than one route of antimicrobial drug administration before, during and after ocular surgery [22]. Hence, the absence of a comparative pharmacokinetic profile for the subconjunctival route for a newer class of drugs makes it difficult to compare it with other routes.

2.4 Intravitreal and subconjunctival injections using drug delivery systems

Considering the amphiphilic nature of liposomes in holding water soluble as well as lipid soluble drugs, it has been evaluated for the extended intraocular pharmacokinetics after intravitreal injection. Intravitreal injection with liposome encapsulation significantly increased the vitreous half-lifes of clindamycin phosphate (3 – 10 hrs) [23], fluconazole (3 – 23 hrs) [24] and amikacin [25]. Intravitreal injection of liposome-encapsulated tobramycin showed vitreous levels above MIC_{90} of *Pseudomonas aeruginosa* even 18 days after administration in rabbits [26].

Following the commercial success of liposome–amphotericin B for systemic fungal infections, the intravitreal administration of liposome-encapsulated antibiotics and antiviral drugs for acute toxoplasmosis retinochoroiditis, presumed *Propionibacterium acne* endophthalmitis after cataract surgery and presumed cytomegalovirus retinitis associated with AIDS have gained interest. A preliminary clinical study also reported that a single intravitreal dose was effective in the treatment of all above conditions [27]. Assil and co-workers [28] compared 24 doses of hourly topical fortified tobramycin therapy with a single subconjunctival administration of multi-vesicular megaliposome-encapsulated tobramycin and free subconjunctival tobramycin in treating a rabbit model of keratitis caused by *P. aeruginosa*. In this study hourly topical fortified tobramycin dosing for 24 hrs was equivalent to single subconjunctival multi-lamellar vesicles (MLV) with tobramycin. Liposome encapsulation was reported to reduce the retinal toxicity of drugs like amphotericin B [29] and fluconazole [30]. Liposome formulation for intravitreal injection was reported to be safe with ciprofloxacin [31], ofloxacin [32] where *per se* ciprofloxacin and ofloxacin did not produce any significant retinal toxicity. In contrast, liposome encapsulation reportedly reduced intraocular antimicrobial efficacy for amphotericin B [29], clindamycin [33] and fluconazole [34]. Liposome formulations were found to be safe for the retina and showed a reduction in drug toxicity. This could be due to the slow release of the enclosed drug instead of reaching higher concentrations immediately following intravitreal injection. This process decreases the incidence of rapid exposure of a higher concentration of the drug causing retinal toxicity. However, reduced antimicrobial efficacy, other formulation factors and sterility are factors restricting its usage.

Although very few studies are available to show the effect of vitrectomy on the clearance of intravitreally injected drugs, the option to use vitreous substitutes that may delay the clearance of intravitreally injected drugs was considered as a therapeutic choice. A study suggested that sodium hyaluronate can be a substitute of vitreous and maintain the half-life of gentamicin [35]. However, further supporting studies using vitrectomy models do not reveal whether hyaluronate is capable of decreasing the rapid clearance of all classes of drugs by acting in a similar way to vitreous. Therefore, the applicability of vitreous substitutes, along with newer antimicrobial agents, needs further investigation. This is also a potential domain to undertake drug delivery interventions for better microbial combat. **Table 1** enumerates the advantages and limiting factors of various delivery systems adopted for the injectable use of antimicrobial agents.

2.5 Intraocular lens as a drug reservoir

This approach is similar to the intracameral application of antimicrobial agents at the end of cataract surgery. It makes intraocular lenses a potential drug eluting material; thereby prolonged drug levels are expected in the aqueous humor to decrease post-operative endophthalmitis. One study evaluated the ability and safety of a hydrophilic acrylic intraocular lens (IOL) as a drug delivery system for gatifloxacin and moxifloxacin in rabbits. This study reported the higher aqueous humor levels of the fluoroquinolones which were eluted from 24 hrs presoaked IOLs in respective fluoroquinolone solutions implanted in rabbit eyes as compared to their topical application as eye drops. Moreover, no eye showed any signs of clinical toxicity [36]. Even though it is an interesting approach, further studies are required to evaluate its clinical superiority to replace intracameral application of antimicrobial therapy as a prophylactic measure in patients undergoing cataract surgery.

2.6 Minipump delivery of antibiotics

The minipump delivery system was compared with standard intravitreal injection of gentamicin sulphate in the *Staphylococcus aureus*-induced model of endophthalmitis. This study evaluated the elimination of microorganisms by comparing intravitreal administration of 100 μg of gentamicin sulfate by either single pars plana injection or the continuous 4-day administration of drugs into the vitreous via pars plana tubing connected to the minipump implanted subcutaneously near the rabbit's ear [37]. Although this system can deliver the drug at a constant rate for a prolonged period, invasiveness and technicality are factors that restrict its further development for clinical use.

3. Topical drug therapy for corneal infections

It is known that drug penetration across the normal cornea is low as compared to the cornea with epithelial defect, due to keratitis. When an avascular tissue like cornea becomes infected, the microbes growing inside the epithelial layers and microbial enzymes start lysing the epithelium and stroma.

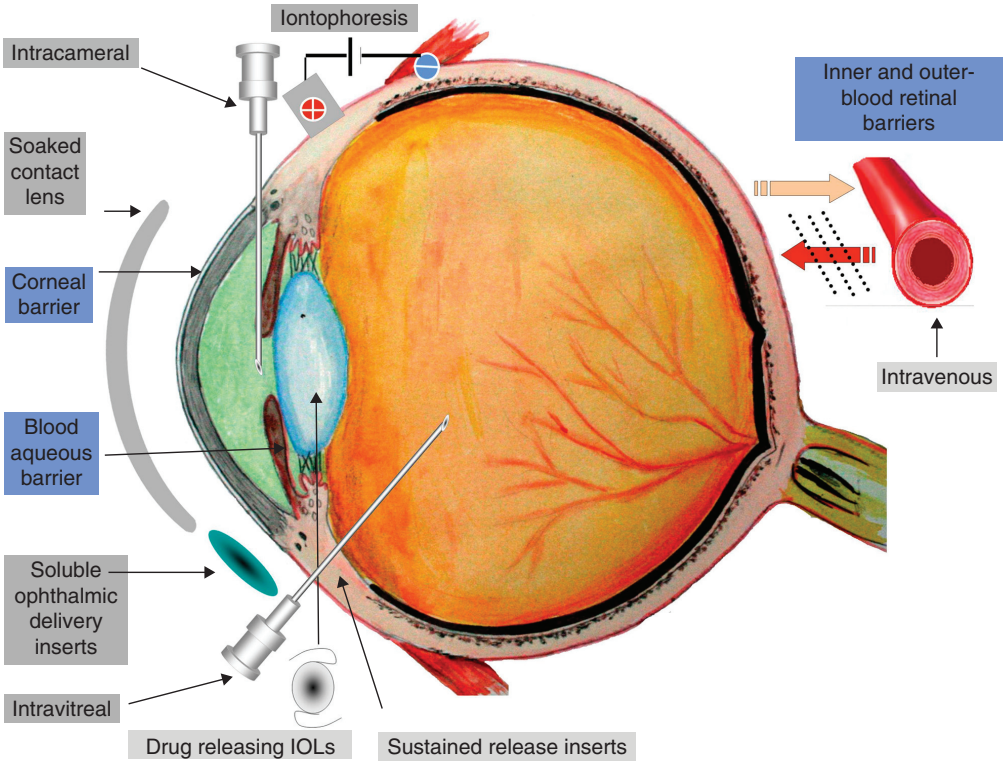

Figure 1. Drug delivery strategies utilized for the delivery of antimicrobial agents.

As a result microbial metabolites and tissue destruction causes release of inflammation mediators which in turn cause vasodilatation of conjunctival blood vessels, leading to red eye. In this process the normal physiology is disturbed and the cornea becomes more sensitive, as it is inflamed. Under the influence of this condition continuous lacrimation and dilated blood vessels of the conjunctiva are capable of rapidly removing the applied drug dosage from the precorneal area. Unless a drug has adequate physiochemical properties to soak the corneal tissue (which can be evidenced by its intraocular penetration), reaching effective MIC_{90} for the invading microbe, along with adequate exposure time, may not be achieved. Apart from this the microbial metabolites and tissue destruction products are also capable of binding to the drug, which makes it inactive. The drugs with sufficient corneal penetration causing adequate levels in the aqueous humor give the theoretical advantage of prophylaxis during cataract surgery, preventing intraocular infection. However, reaching vitreous humor via topical therapy is not a viable option currently with the present antimicrobials.

3.1 Particulate drug delivery systems as topical drug carriers: liposome, solid lipid nanoparticles and nanoparticles

Water soluble penicillin G and water insoluble indoxole-loaded liposome instillation have been reported to increase the drug flux across the rat cornea as compared to the drug applied using polysorbate-80 [38]. Moreover, positively charged liposomes showed better penetration as compared to negatively charged liposomes. The proof of the concept of positively charged liposomes interacting with the cornea came from a study conducted to visualize the interaction on rat cornea. This study reported that the interaction of liposome entrapped propidium iodide and horseradish peroxidase (which is impermeable to epithelium) on the outer epithelium of the rat cornea after specific processing [39]. It was reported that topical application of liposome formulation is capable of increasing the intraocular penetration of ciprofloxacin [40]. In contrast, single unilamellar vesicles (SUVs) lack pharmaceutical stability, making them unsuitable for recurrent applications from the time of reconstitution. Study results from our laboratory show the leakage of dipicolinate from the aqueous compartment of SUVs, evidenced by the formation of terbium–dipicolinate complex outside the liposome (indicated by increasing fluorescence) along with time (**Figure 2**). A single topical application of tobramycin (3.5 mg/0.1 ml) multi-vesicular liposomes enmeshed in a fibrin sealant with an overlaying bandage contact lens was studied in the model of *Pseudomonas keratitis* in rabbits and showed that this method comparatively decreased the bacterial count in the cornea [41].

Solid lipid nanoparticles (SLN) as carriers for topical ocular delivery of tobramycin have been reported [42]. It was found that when compared with an equal dose of aqueous

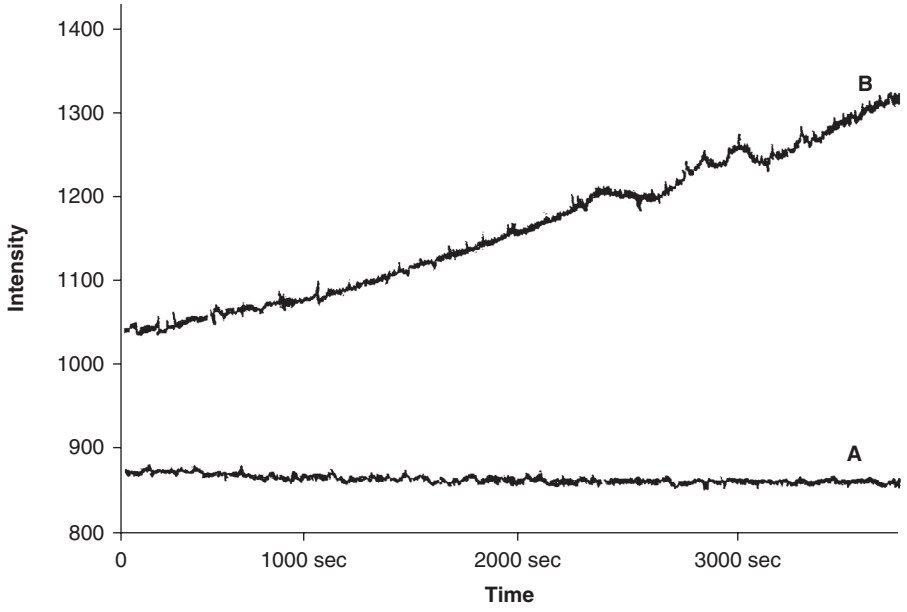

Figure 2. Increase in the intensity of fluorescence of dipicolinate–terbium complex formed when dipicolinate leaked from the liposomes at room temperature. Dipicolinate containing positively charged single unilamellar liposome made with the molar lipid ratio of 7:2:1:1 for soy lecithin, cholesterol, α-tocopherol and stearylamine respectively using extrusion technique. (**A**) No increase in fluorescence of terbium added to the empty liposomes. (**B**) Increase in fluorescence when the leaking dipicolinate complexed with terbium, thereby increasing fluorescence along with time (unpublished data).

tobramycin eye drops, tobramycin containing SLNs produced a significantly higher bioavailability in the aqueous humor. Furthermore, polycyanoacrylate nanoparticles were loaded with amikacin sulphate and evaluated for their ability to improve the corneal penetration of this hydrophilic drug. This study reported the significant increase of amikacin concentration in the cornea and aqueous humor in nanoparticle formulation as compared to the control solution [43]. All the above attempts used freshly prepared particulate drug formulations in the form of liposomes, solid lipid nanoparticles and nanoparticles, which are capable of increasing the transcorneal penetration of drugs. However, it is not convenient for a patient to reconstitute when necessary for repeated applications. In aqueous form they tend to release the enclosed drug, thereby their shelf life is highly compromised. Therefore these approaches face practical difficulties in pharmaceutical aspects for their intended mass usage.

3.2 Soluble ophthalmic delivery inserts

Soluble ophthalmic delivery inserts (SODI) have been extensively investigated to enhance the corneal drug delivery of aminoglycoside, cephalosporin, fluoroquinolone antimicrobials and anti-inflammatory agents. These systems were found to be beneficial for lubrication, drug delivery, corneal protection and re-epithelialization. Due to its biocompatibility and well-established safety profile, collagen represents a favorable matrix for ocular drug delivery. Collagen polymer containing ^{14}C-gentamicin was studied for its usefulness in delivering radio-labeled gentamicin in rabbits [44]. After taking tear film, multiple corneal and scleral biopsies, it was concluded that this wafer route of administration gave the highest tear film and tissue concentration of drugs, even compared to subconjunctival injections. Further studies supported this approach by evaluating the pharmacokinetic profile of gentamicin collagen film [45]. Similarly, a collagen-based approach gained quick importance for the delivery of dexamethasone and kanamycin [46], netilmicin [47], vancomycin, or a combination of both vancomycin and gentamicin [48].

The advantages of collagen shields soaked with tobramycin [49] and amphotericin B [50] over eye drops have been reported in animal models. Apparently, they did not affect the mechanisms of the corneal wound healing process [51]. In a *P. aeruginosa* induced keratitis model in rabbits, ciprofloxacin-soaked collagen shields were more effective as compared to norfloxacin and tobramycin [52]. Although collagen shields increased the aqueous penetration of topically applied gentamicin, they failed to increase the vitreous penetration, even after bilateral lensectomy and vitrectomy in rabbits [53]. Wang and co-workers [54] evaluated collagen shields on the permeation of cephradine and reported that it increased the aqueous levels up to 1.5 times in intact and 1.3 times in defective corneal epithelium versus control. This study also reported that as compared to soft contact lenses, collagen shields offered increased aqueous humor levels. Interestingly, another study with netilmicin showed that collagen shields need not to be soaked with a very high concentration of drug for its extended release [47]. As compared to non-cross-linked collagen discs, cross-linked collagen shields absorbed more

gentamicin with prolonged soaking time and two hours presoaked discs completely dissolved within 6 min after being placed in the lower fornix of the rabbit eye [55]. Therefore, cross-linking of collagen achieved an extended stability and release kinetics of ofloxacin up to 24 and 72 hrs [56]. The antibiotic–hydrogel inserts made with copolymers of N-vinylpyrrolidone molded into an ocular insert and impregnated with erythromycin or erythromycin estolate were reported to completely suppress the *Chlamydia trachomatis* infection in the owl monkey eyes [57].

To clarify the role of corneal collagen shields as a drug delivery device for the treatment of bacterial keratitis, a comparative study evaluated the effectiveness of topical gentamicin treatment, with and without the use of corneal collagen shields, in a rabbit model of *P. keratitis*. This study did not find any difference between the groups that received a loading dose of antibiotic drops at the beginning of treatment, either with or without an antibiotic-impregnated collagen shield. This study further suggested that antibiotic-impregnated collagen shields should not replace traditional antibiotic drop therapy as the mainstay of treatment, but may be a useful adjunct to treatment with topical antibiotics [58].

Collagen shields containing a mixture of antibiotics and anti-inflammatory agents were also evaluated and found to be safe in patients undergoing various treatment modalities of the eye [59,60]. The efficacy of presoaked porcine collagen shield was compared with subconjunctivally injected corticosteroids and antibiotics in reducing ocular inflammation after extra-capsular cataract extraction with intraocular lens implantation. Patients who received a 24 hr shield presoaked with 0.1% betamethasone disodium phosphate and 0.5% netilmicin and the patients who received 1 mg betamethasone disodium phosphate and 250 mg piperacillin as a subconjunctival injection showed no significant differences in the parameters considered. However, this study observed a transient, slight diffuse superficial corneal edema in 24% of the collagen shield group as compared to 4% in the subconjunctival group. This study also raised concerns over oxygen transmission through collagen shields under closed eyelids [61].

Three patients suffering from *aspergillus keratomycosis* were treated with collagen shields containing amphotericin B (soaked with 0.5% for 2 hrs at 25°C). These shields were replaced daily and used in conjunction with amphotericin B (0.25%) eye drops, which were applied every 2 hrs. Cultures from the eyes of all patients became negative within 15 days of treatment [62].

A prospective, randomized study evaluated the aqueous penetration of tobramycin in 32 patients undergoing cataract surgery. The subjects were divided into two groups, the first group received three preoperative drops of the commercially available combination of tobramycin–dexamethasone at 15 min intervals. In the second group a collagen shield soaked in the same medication was applied to the eye prior to surgery. This study reported that the mean aqueous concentration of tobramycin was not statistically significant in both groups to reach MIC_{90} for common ocular pathogens [63]. Similarly when ofloxacin 0.3% was studied, it was found that a collagen shield increased the ofloxacin penetration to three times that of eye drops, but the levels were above MIC_{90} of most of the common ocular pathogens [64].

Moxifloxacin 0.5% was administered before vitrectomy surgery in 10 patients using a 24 h dissolvable cross-linked corneal collagen shield delivery device. Interestingly in this study, aqueous penetration of moxifloxacin via collagen shield was reported to be lower than topical drops [65]. Similarly, Haugen *et al.* [66] reported the use of collagen shields presoaked in fourth-generation fluoroquinolones compared with conventional topical prophylaxis in the rabbit endophthalmitis model. This study concluded that topical therapy with gatifloxacin before and after intraocular bacterial challenge led to lower incidences of endophthalmitis in rabbits. Prophylaxis with presoaked collagen shields was not statistically different to that of topical drops.

The hydrophilicity of the aminoglycoside antibiotics made them less penetrating across the hydrophobic epithelium of the cornea and they cleared from precorneal area at a fast rate. This process resulted in low levels of aminoglycoside in the aqueous humor. Soluble collagen shields were extensively studied and were reported to increase the transcorneal permeability of aminoglycoside antibiotics. The application of hydrophilic collagen shields slowed down their precorneal clearance, thereby increasing the intraocular penetration. When it comes to newer fluoroquinolone antimicrobials, collagen shields are not very promising due to the improved molecular characteristics of these agents, especially the fourth generation fluoroquinolones, with comparatively low MIC_{90} values for most of the ocular pathogens. Therefore, the applicability of collagen shields with newer antimicrobial agents with low intraocular penetration needs further investigation.

3.3 Contact lenses as drug reservoirs

Contact lenses were extensively studied as drug reservoirs due to their commercial availability and affordability. Hydrophilic contact lenses were used as a different modality and a comfortable therapeutic approach for the topical use of chloramphenicol and tetracycline [67]. Robin and Ellis [68] showed increased aqueous penetration of gentamicin in rabbit eyes fitted with hydrophilic contact lenses soaked in gentamicin solution. Hydrophilic soft contact lenses with increased water content positively correlated with the intraocular penetration of tobramycin in rabbits [69]. One study used Morgan therapeutic contact lenses (The Morgan Lens and MorTan Inc, Missoula, MT, USA) to perfuse gentamicin for 4 hrs in rabbits and reported that the levels produced were equivalent to the levels of every 15 min gentamicin eye drop application [70].

In patients undergoing cataract surgery, a study estimated the aqueous concentrations of chloromycetin, gentamicin, or

carbenicillin administered either subconjunctivally or through drug-soaked soft contact lenses. This study showed that soft contact lenses provided significantly higher drug penetration than subconjunctival therapy. Both modes of treatment provided therapeutically effective levels against most of the common ocular pathogens for varying intervals of 2 – 12 hrs [71]. A human study analyzed the usage of hydrogel bandage contact lenses (61.4% HEMA and 38.6% water content) soaked overnight with preservative-free gentamicin in 10 volunteers. This study reported the existence of tear film concentration of gentamicin up to 96 hrs. The investigators reported that this method was capable of holding bactericidal concentration of gentamicin more than 1.6µg/ml over the period of 3 days [72]. Subsequently, disposable single use contact lenses were studied for their suitability to deliver lomefloxacin to rabbit eyes [73]. The contact lenses soaked in 0.3% lomefloxacin were reported to release sufficient amounts of lomefloxacin to reach higher levels in both the cornea and aqueous humor as compared to frequent-drop therapy for up to 8 hrs. Further studies also proved that there is a variation in the release profile of fluoroquinolone antimicrobials in different brands of contact lenses [74].

A prospective study evaluated the transcorneal penetration of five topically applied aminoglycosides and fluoroquinolones into the aqueous humor of patients. This study assessed gentamicin, kanamycin, tobramycin, ciprofloxacin and ofloxacin either by using a contact lens or eye drop. It was observed that the among the aminoglycosides tested, only gentamicin and tobramycin, but not kanamycin, were able to penetrate into the aqueous humor of patients. Interestingly, a similar amount (0.3%) of drug-soaked contact lenses reached mean aqueous levels of 1.23 and 5.5µg/ml for ciprofloxacin and ofloxacin respectively [75]. Despite the fact that many studies have estimated the aqueous and corneal levels of drugs applied through contact lenses, it is striking that no efforts have been made to quantify the dosage delivered through contact lenses. Therefore, the capability of contact lenses to hold high to moderate hydrophilic drugs cannot be ascertained.

In terms of intraocular penetration, the hydrophilic contact lens might share the same qualities of collagen shields as far as highly water soluble drugs are concerned. As mentioned above, different brands of contact lenses showed a different release profile of lomefloxacin in an experimental study, this indicates that the drug delivery (as far as contact lens is concerned) is highly related to its hydrophilicity (as evidenced by water content). If the material used for contact lens is having altered hydrophilicity its corresponding drug binding can also be altered. Studies using contact lens to deliver fourth generation fluoroquinolones are not available for comment.

3.4 Polymers in topical drug delivery

Enhanced gentamicin topical delivery using polyglucin was reported in 1981 by Kutskaia *et al.* [76]. The role and the concept of mucoadhesive polymers gained much importance after the success of soluble ophthalmic inserts with aminoglycoside antibiotics. Mucoadhesive polymers prolong the precorneal drug residence time and thereby the rapid removal of the instilled eye drop is reduced. Sodium hyaluronate 0.25% used as a vehicle for gentamicin sulphate increases its availability on the ocular surface for at least 10 min. Polycarbophil, a mucoadhesive polymer of the poly(acrylic acid) type, was studied to improve the ocular delivery of topically applied gentamicin. The study compared a neutralized polymer and non-neutralized polymer with aqueous formulation. The results of this study showed that both polymeric formulations increased the uptake of gentamicin by the bulbar conjunctiva. Drug penetration into the aqueous humor was observed only with the non-neutralized polymer, probably occurring via the conjunctival–scleral pathway, facilitated by intensified contact between the mucoadhesive polymer and the underlying bulbar conjunctiva [77].

Mucoadhesive polymers obtained from natural sources were evaluated to increase drug penetration across the cornea. The efficacy of a mucoadhesive polymer obtained from tamarind seed was tested as a delivery system for the ocular administration of hydrophilic and hydrophobic antibiotics. Healthy rabbits were subjected to repeated ocular instillations with either conventional gentamicin or ofloxacin, or these agents viscosified with the tamarind seed polysaccharide. The viscosified formulations increased the drug concentrations both in the aqueous humor and the cornea as compared to their aqueous formulations [78]. The same polymer was used for the ocular delivery of 0.3% rufloxacin in the treatment of experimental *P. aeruginosa* and *Staphylococcus aureus* keratitis in rabbits. The results suggested that the tamarind seed polysaccharide prolongs the precorneal residence times of antibiotics and enhances drug accumulation in the cornea, probably by reducing the washout of topically administered drugs [79]. Prolonged delivery of gentamicin was achieved using a bioadhesive ophthalmic device insert (BODI) in dogs and rabbits [80].

Another study used gelatin as a natural hydrophilic polymer to deliver ciprofloxacin where a rate-controlling membrane was prepared using hydrophobic ethyl cellulose. This formulation reportedly increased the intraocular penetration of ciprofloxacin in rabbits [81]. Positively charged polysaccharide chitosan was studied for its ability to increase the precorneal residence time of ophthalmic formulations. After topical application with the above formulation, tobramycin and ofloxacin were compared with their 0.3% conventional aqueous formulations. This study reported that two chitosan products of high molecular weight (1350 and 1930 kD) and low deacetylation degree (50%) significantly increased antibiotic availability when compared to the control [82]. Chitosan hydrochloride mediated ofloxacin release was studied using erodible inserts based on polyethylene oxide and it was found that the increased corneal penetration achieved for ofloxacin was due to the ability of chitosan hydrochloride to increase the transcorneal permeability [83].

Good tolerance, long intervals of application and an excellent adhesion are the defining features of viscous eye drops (hydrogels). The use of fusidic acid as a hydrogel in the treatment of bacterial eye infections showed a long-lasting antibiotic concentration in tear fluid [84]. A double-blind clinical trial using 26 patients showed that topically administered low molecular weight sodium hyaluronate along with tobramycin decreased the corneal ulcer treatment duration significantly as compared to tobramycin alone [85]. Hydrogel polymers are revealing promising prospects to enhance transcorneal penetration as well as duration of delivery.

3.5 Iontophoresis in the ocular delivery of antimicrobials

Iontophoretic application is the technique which uses low electric currents to drive charged molecules towards the opposite polarity. It is a very convincing technique, however it has not gained popularity due to the fear of electric burns and the lack of universal standardization among different manufacturers about the utility of their probes and drug delivery design. The effects of iontophoretic application of tobramycin on the corneal concentration was compared by Hobden and co-workers [86] in the resistant *P. aeruginosa*-infected and normal rabbit corneas. Corneas infected with *P. aeruginosa* were treated 22 hrs after infection with tobramycin delivered by either iontophoresis, mock iontophoresis (eye cup without current), or application of fortified topical drops. Corneal iontophoresis of tobramycin at 10 mg/ml showed a one log reduction in the number of bacteria per cornea, yielding a significantly lower number of bacteria compared to other treatments [87].

In another study transcorneal and *trans*-scleral iontophoresis were compared to subconjunctival injection in the delivery of gentamicin into rabbit eyes. This study assessed the potential corneal toxicity of *trans*-corneal iontophoresis by measuring corneal thickness and endothelial cell counts before and 3 days after *trans*-corneal iontophoresis of gentamicin; balanced saline solution served as control. It is of interest that this study showed no significant toxicity among the groups [88]. Corneal iontophoresis using soft stable hydroxyethyl methacrylate hydrogel discs (80% water content) loaded with gentamicin sulphate which were mounted on an iontophoresis probe was reported by Frucht-Pery *et al.* [89] in rabbits. This study reported that a current of 0.6 mA used for 60 sec significantly increased the *trans*-corneal permeation of gentamicin. As fluoroquinolones have the advantage of having an established key role in ophthalmic therapeutics, using iontophoresis with more cumbersome efforts to achieve antimicrobial concentration in the aqueous humor becomes unattractive.

3.6 *In situ* gel forming matrix for extended drug release

Hydrogen ion (pH) dependent *in situ* gel forming matrix to elute ofloxacin was developed with the help of polyacrylic acid as the gelling agent in combination with hydroxypropyl methylcellulose which acted as a viscosity builder. This matrix was reported to be therapeutically efficacious, stable, non-irritant and provided sustained release of the drug over a period of 8 hrs [90]. An ophthalmic delivery system of pefloxacin mesylate was prepared using the concept of ion-activated *in situ* gelation. Gelrite gellan gum, which gels in the presence of mono or di-valent cations present in the lacrimal fluid, was used as the gelling agent. The aforesaid formulation was compared with marketed eye drops to evaluate its efficacy for the treatment in the experimental model of bacterial conjunctivitis in rabbits. The formulation demonstrated better therapeutic efficacy as compared to standard eye drops [91]. In the microbial infected, inflamed eye, the safety and efficacy of this system needs to be addressed before accepting that this method is suitable for future ocular topical drug delivery.

3.7 Ointments

Ophthalmic ointments were extensively studied as formulations in the initial development of drugs for ophthalmic infections. The use of ointments as an ocular drug vehicle added an important dimension to topical therapy as ointments are well tolerated, fairly safe and provide an excellent means for enhanced ocular contact time, thereby increasing ocular drug levels [68]. Hardberger *et al.* [92] reported that tetracycline levels in the corneal epithelium, aqueous humor and lens were markedly elevated by increasing the drug concentration and the drug contact time with the eye. An ocular kinetic study revealed that topical ointment and the subconjunctival injection route produced bacteriostatic concentrations of chloramphenicol in the aqueous humor lasting for several hours, as compared to powder and i.v. routes [93]. Mass treatment of entire communities with tetracycline eye ointment is a method reported for the treatment of hyperendemic trachoma [94]. Acyclovir ointment (3%) reached the C_{max} of 3.38 µg/ml at the T_{max} of 60 min and C_{max} of 45.78 µg/ml at the T_{max} of 30 min in aqueous humor and cornea respectively [16]. Ointments still hold promise to increase the precorneal residence time of drugs, however, the discomfort induced by their application is a major limiting factor which restricts their use only to time spent asleep. Moreover, the ointment formulation might reduce the effect of concurrent administration of other eye drops.

3.8 Wicks as drug reservoirs

Employing wicks as drug reservoirs was highlighted by Ong-tone [95] for the usage of preoperative mydriatics for cataract surgery. In their hospital set-up traditionally five drops were used for dilating pupils, namely proparacaine 0.5%, cyclopentolate 1%, phenylephrine 2.5%, flurbiprofen sodium 0.03% and ofloxacin 0.3% at 15-min intervals given three times. As this requires intensive nursing care, they started using a wick soaked in the above mixture and reported that it significantly reduced the workload of the hospital staff. The same investigator further attempted a similar approach

to determine the penetration of gatifloxacin and moxifloxacin into the aqueous humor. This study reported that moxifloxacin penetrated the aqueous humor better than gatifloxacin when given in wick soaked in the dilating mixture before cataract surgery. The penetration of moxifloxacin increased significantly when its concentration was doubled in the dilating mixture. In both groups, only moxifloxacin reached and exceeded the minimum inhibitory concentration levels for most of the common ocular pathogens causing endophthalmitis. In this study the aqueous moxifloxacin levels reached the extent of 1.34 ± 0.8 μg/ml, which is above the MIC_{90} of common ocular pathogens [96]. Therapeutic wicks to deliver multiple drugs remain today as an individualized approach to solve the problems associated with the administration of many eye drops together. A mixture of eye drops can make drastic changes in the corneal penetration due to the alteration in the pH of the resultant mixture and osmolarity. A rational selection of likely components complementing each other and mutually enhancing corneal transfer would be highly beneficial in such approaches, instead of making an indiscriminate cocktail of two or more drugs. **Table 2** compares the advantages and limitations of various systems adopted for the topical delivery of antimicrobial agents.

4. Miscellaneous approaches

4.1 Altering the drug transporters in ocular barriers

Drug transport in the eye is regulated by blood–ocular barriers in which the presence of transporters is well recognized. Permeability restriction offered by the blood–retinal barrier (BRB) is reported to play a major role in the drug therapy in endophthalmitis as it limits the entry of antibiotics into the affected site as a prophylactic measure or immediate defense. In the BRB, the presence of inner and outer blood retinal barriers (iBRB and oBRB) has also been well recognized [97]. The oBRB is formed by the retinal pigment epithelium. The tight junctions in the epithelium enable the formation of a barrier by joining the neighboring cells together and regulating transepithelial diffusion through the paracellular spaces [98]. The retinal capillary endothelial cells connected to each other by tight junctions play a key role in permeability as the iBRB [99]. Therefore, vitreous levels of drugs are determined by both iBRB and oBRB together. Efflux pump like P-glycoprotein (P-gp) is known to be a major barrier to drug delivery. Functional P-glycoprotein has been recently identified in the cornea and corneal cell lines. Therefore, blocking the efflux transporters to achieve higher vitreous levels of intravenously injected drugs or reducing the retinal efflux when they are injected intravitreally are the strategies exploited.

The effect of P-gp modulation on the disposition of ofloxacin at the blood–ocular barriers was studied using gamma scintigraphy. The BRB efflux of intravitreally injected radio-labeled ofloxacin was reduced by pretreatment with verapamil [100]. In a study, anesthetized rabbits were given constant topical infusions of ^{14}C labeled erythromycin in the presence and absence of inhibitors. Among the blockers tested, verapamil inhibited the efflux pump with moderate change in $AUC_{(0-\infty)}$ and Cmax as compared to control. This study concluded that ocular bioavailability of P-gp substrates can significantly be enhanced by proper selection of P-gp inhibitors [101]. This field of research is presently striving to gain further understanding of the positioning of transporters present in the cornea and retina and the effect of their modulation to increase the intraocular penetration of drugs. These transporters have a defined physiological role in the extrusion of various nutrients and metabolites in and out of the eye. Therefore, the effect of their blockade on ocular safety is of great concern before accepting them as a therapeutic strategy.

4.2 Prodrugs

A study evaluated the prodrug of ganciclovir for oligopeptide transporter-targeted *trans*-scleral drug delivery to rabbit retina. This study concluded that due to higher lipophilicity and through an oligopeptide transporter mediated mechanism, dipeptide monoesters of ganciclovir translocated themselves across the retinal pigment epithelium. Therefore, they appear to be promising candidates in the treatment of ocular cytomegalovirus infections following an episcleral administration [102]. Similar to the concerns of the transporter blockers above, further studies are required to establish the safety of prodrugs by this oligopeptide transporter mechanism.

Various alkylcarbonyloxymethyl esters of nalidixic acid ranging from 3 to 15 carbon units in the pro-moiety have been prepared and assessed as potential prodrugs. Their chromatographic retention factors k′, silicone oil solubilities and *in vitro* conversion to nalidixic acid by a commercial esterase were determined, together with their *in vitro* antimicrobial activity and cytotoxicity in a study. The preliminary results suggested that silicone oil may have the potential for the effective intra-ocular delivery of antibacterial compounds [103].

4.3 Sustained release inserts for prolonged antiviral therapy

Cytomegalovirus (CMV) retinitis is the most common AIDS-related ocular opportunistic infection and can develop in up to 40 – 50% of AIDS patients prior to the initiation of Highly Active Anti-Retroviral Therapy (HAART) [104]. In order to achieve an alternative for other modes of conventional therapy, an intravitreal sustained release implant of ganciclovir has been developed (Vitrasert: Chiron Vision Corp. Irvine, CA, USA). It is placed surgically in the posterior segment of the eye and allows diffusion of the drug locally to the site of infection over an extended period of months. This polymeric device, containing 4.5 mg ganciclovir, is reported to deliver 0.2 – 1.6 μg/ml of ganciclovir for a period of 6 – 8 months and it has to be replaced with a new implant to meet the therapeutic necessity.

However, the successful outcome of this implant depends upon various factors like MIC_{90} of CMV (if the MIC_{90} of the virus exceeds the release rate of the device) and problems associated with intraocular surgery to place this sustained release implant into the vitreous cavity. This includes vitreous loss, vitreous hemorrhage, cataract formation, retinal detachment, uveitis, endophthalmitis and decrease in visual acuity. In most of the cases immediately following implantation, patients experienced an immediate and temporary decrease in visual acuity in the implanted eye which lasted for approximately 2 – 4 weeks post-operatively. Post-mortem findings reported fibrous 'in-growth' in the place of implantation, which seemed to be a benign occurrence because of its limited extension in most of the eyes studied. Microscopic vitreous hemorrhage was present in many eyes, especially those that underwent multiple procedures [105]. However, after the initiation of HAART the incidence of CMV retinitis considerably reduces due to substantial increase of CD_4 counts in AIDS [106]. However, this implant mode of delivery holds promise for the localized treatment of CMV retinitis for a prolonged period to avoid systemic toxicity of ganciclovir and repeated intraocular injections for prolonged periods [107]. Although this kind of drug delivery has been extensively used in other ocular pathological conditions [108], adopting it for ocular antimicrobial use is subject to the requirement of drugs warranting prolonged release in the vitreous.

5. Conclusion

The scientific gains obtained from the endophthalmitis studies like EVS and ESCRS clearly indicate that prophylactic use of antibiotics can reduce post-operative endophthalmitis in patients undergoing ocular surgical manipulations. However, achieving an effective antimicrobial concentration of a wide spectrum drug by conventional oral or topical route is limited by the barrier functions of the eye. Drug delivery systems used to overcome the hurdles using advanced pharmaceutical technology also have many limitations. As there is a paradigm shift in the class of antibiotics used in clinical practice, conventional aminoglycoside antibiotics are being replaced by fortified preparations, newer generation antimicrobials like fluoroquinolones and others. Still the antifungal and antiviral management is limited by suboptimal ocular penetration and poor sustainability of their levels in ocular tissues. The availability of a new antimicrobial class of compounds like fluoroquinolone, echino or pneumocandin anti-fungals with chemically diverse molecular structures with differential hydrophobicities render many of the previously studied attempts like collagen shields and contact lenses unusable as a common media for drug delivery. Attempts made to use liposomes and nanoparticles also showed several limitations and reduced efficacy. Moreover, approaches like iontophoresis, *in situ* gels, minipumps and drug-soaked wicks are in need of further studies before their utility for clinical use can be accepted. Among the present approaches, polymeric drug delivery to overcome barriers, drug eluting IOLs, along with newer drugs and transporter-mediated smart drug delivery are promising approaches.

6. Expert opinion

Antimicrobial drugs are primarily developed for various systemic microbial infections based on their pharmacokinetic/dynamic correlation. Conventionally, they are re-investigated for ocular use without much scientific exploration of their ocular penetration characteristics and rationale. The prophylactic and therapeutic strategies for ocular infections are very different from other systemic microbial diseases. In my opinion ocular drug therapy so far remains as an arbitrary approach where drug molecules inherently lacking in ocular penetration capabilities are forced to enter the eye with the help of pharmaceutical drug delivery techniques.

Antibiotics such as aminoglycoside, penicillin and cephalosporin already had oral absorption problems and were administered using injectable routes. Therefore, hydrophilic collagen shields were extensively investigated to enhance their transcorneal penetration. Collagen shields are not encouraging when it comes to increasing the penetration of a newer generation of antimicrobials like fluoroquinolones. The xenobiotic permeation barriers present in vital parts of the human body play a guarding role and share a sort of common substrate selectivity. Therefore, achieving drug concentration beyond their control in the protected organ cannot depend only on normal delivery systems. More studies are required to understand the stage-by-stage ocular response while a microbe is multiplied inside the aqueous or vitreous cavity. In systemic infections, immediate recognition of microbial entry and immune-mediated responses result either in successful elimination of the invading microbes or are exhibited as symptomatic manifestations. In contrast, the lack of instant immune response in the humors of the eye facilitates multiplication of the invading organism without any palpable manifestation unless the microbial load reaches a critical mass. At this stage the microbes and their metabolites are capable of creating inflammation and breaching the ocular barriers, posing a greater challenge for antimicrobial therapy. Removal of vitreous in the posterior segment by pars plana vitrectomy is the only way to reduce the microbial load instantly. Therefore, it is expected that a successful drug or drug delivery must characteristically differ between its prophylactic or curative use.

7. Prophylactic antimicrobial delivery

This can be achieved by either topical application or systemic administration. In both attempts clear molecular strategies need to be adopted for the development of a drug with very low levels of MIC_{90} for the target microbes. Ocular drug absorption characteristics need to be assessed based on molecular dynamic principles and a favorable

molecular modeling approach must be used to design drugs for ocular use. To redefine optimum molecular constructs for a particular group of compounds for intraocular penetration, their Quantitative Structure Property Relationship (QSPR) needs to be established. Considering the vital importance of sight saving attempts, this approach must undergo systematic evaluation to reach a higher concentration inside the eye. To accomplish this objective, molecular drug delivery strategies can be adopted.

The newly developed eye-specific drug is expected to use smart drug delivery strategies based on physiological mechanisms for their selective enrichment inside the eye. For example, intraocular ascorbic acid levels are many times higher than plasma levels and this process is mediated by a selective tricarboxylic transporter mechanism. Interesting attempts are already in place for drugs like ganciclovir using oligopeptide transporter after episcleral administration. Identification of drug transporters in ocular barriers and knowledge about the recognition pattern of structurally diverse compounds can aid us to strategize ocular drug delivery for prophylactic measures.

8. Post-infection antimicrobial delivery (curative)

In a frank endophthalmitis, a microbial mass reduction strategy must be adopted at any cost to reduce microbial load and their metabolites by vitrectomy. It is usual practice in ophthalmology to give vitreous temponade either by silicone oil or using therapeutic gases. This practice offers an excellent opportunity for the use of polymer-embedded antimicrobials. Either the polymer is attached with an antimicrobial agent via a spacer, which is susceptible to microbial enzymes, or the polymer is made capable of eluting the antimicrobial agent in a sustained manner. Certain ethylene oxide-propylene oxide co-polymers are known to inhibit the efflux activity of transporters. These kinds of polymers can also be used with antimicrobial drugs for intravitreal or intracameral injection to decrease the rate of drug clearance. Development of non-invasive monitoring of the ocular drug levels by using Raman spectroscopy is an upcoming field, expanding the scope of indirect drug measurements in the eye for future therapeutics.

Among the present approaches, drug eluting intraocular lenses are a promising and rational approach to prevent post-operative cataract surgery infections. In this approach, rather than changing lens material for drug delivery, drug molecules can be optimized to bind directly or by using a polymer coat on the IOLs. This strategy might increase the chances of getting ideal intraocular delivery characteristics for the release of antimicrobial drugs in the initial few hours after cataract surgery to prevent endophthalmitis. Before directly putting these IOLs to human use, a pragmatic pharmacokinetic versus dynamic correlation study is essential.

Lack of enthusiasm in pharmaceutical companies, which are forced to target a limited population of specialists to execute complicated ocular antimicrobial drug delivery systems with surgical interventions is another relevant issue to be considered. A mass utilitarian approach using simpler techniques would be hugely appreciated in this commercial perspective. To conclude, an ocular-specific antimicrobial agent along with an appropriate drug delivery approach is expected to revolutionize future therapy for ophthalmic infections.

Declaration of interest

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