

apdrops dx

EYE DROPS

Moxifloxacin 0.5% + Dexamethasone 0.1% w/v

The D-Xtra Power

Product Monograph

1st
Time in IRAQ



apdrops dx

EYE DROPS

Moxifloxacin 0.5% + Dexamethasone 0.1% w/v

D-Xtra

The Power against Infection & Inflammation



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Section I

Ocular inflammation and infections – Clinical review

Ocular inflammation and infections

Red eye is the cardinal sign of ocular inflammation with conjunctivitis being the most common cause of red eye. Other common causes of ocular inflammation include blepharitis, corneal abrasion, foreign body, subconjunctival hemorrhage, keratitis, iritis, glaucoma, chemical burn, and scleritis.¹ Bacteria are the major contributor of ocular infections worldwide. Bacteria are generally associated with many types of ocular infections such as conjunctivitis, keratitis, endophthalmitis, blepharitis, orbital cellulitis and dacryocystitis. Both Gram positive and Gram negative bacteria are threats of ophthalmic tissues. However, Gram positive bacteria are the major contributor of ocular infections. Because there is no specific diagnostic test to differentiate viral from bacterial conjunctivitis, most cases are treated using broad-spectrum antibiotics. Ocular infections, if left untreated, can damage the structures of the eye leading to visual impairments and blindness.²

Spectrum of ocular infections

1. Conjunctivitis

Conjunctivitis, inflammation of the mucosa of conjunctiva, is the most frequent ocular case with noticeable economic and social burdens. During chronicity, the disease can affect not only the conjunctiva but also adjacent structures including the eye lid and can be a potential risk for other extra or intraocular infections. Bacteria contribute for about 50–70% of infectious conjunctivitis.

2. Blepharitis

Blepharitis which is an inflammation of the eyelid can cause loss of eye lash. The infection may not remain localized and is known to spread to other anatomical sites of the eye. Keratitis, the most serious eye infection is the leading cause of corneal blindness. Moreover, the disease can also progress to endophthalmitis if not diagnosed early.

3. Dacryocystitis

Dacryocystitis is an inflammation of the nasolacrimal duct. During chronicity the disease is associated with infection, inflammation of the conjunctiva, accumulation of fluid and chronic tearing. This can be potentially dangerous to ocular tissues such as the cornea; leading to post surgery endophthalmitis.

Post-surgical ocular inflammation and infections

Despite advances in surgical techniques and modern day technologies, inflammation after complex ocular surgery continues to be a burden for both patients and physicians. Postoperative ocular inflammation is a well-known phenomenon and response to surgical trauma and appears to occur independently of the type (eg, vitreoretinal or combined glaucoma surgeries) and severity. Post ocular-surgery complications are vision threatening, hence it's important to treat this with right treatment.

Types of post ocular complications

Exogenous endophthalmitis

Exogenous endophthalmitis is an infective complication of primary cataract, intraocular surgery and ocular trauma due to the introduction of infectious bacterial pathogens, whereas endogenous endophthalmitis is commonly due to systemic dissemination of the pathogens. Both keratitis and endophthalmitis are potentially devastating ocular infections if not diagnosed early. 90% of postoperative endophthalmitis occurs following cataract surgery.

Post lasik infectious keratitis

Infectious keratitis following refractive surgery can be placed into 2 categories: 1) early-onset (within the first 2 weeks of surgery) and 2) late-onset (which can occur from 2 weeks to 3 months following surgery). Infectious keratitis after LASIK is a potentially vision-threatening complication.

Common bacterial isolates in ocular infections

Identification of the causative agent is important as resistance to all conventionally used antibiotics is increasing. In a study, the culture analysis of conjunctival swabs showed that 41% were cultured positive with gram positive bacteria, of which *Staphylococcus aureus* (52.5%) and *Staphylococcus epidermidis* (30.1%) and Micrococci (8.3%) were seen. Only 9.1% were culture positive with gram negative, of which *Klebsiella pneumoniae* (5.14%) and *Pseudomonas aeruginosa* (2.6%) and others (*Acinetobacter*, *Haemophilus*, *E. coli* and *Moraxella*; 1.36%) were seen keeping in view the increasing use of contact lens and unclean fingers.

The percentage resistance profile of gram positive isolates showed cefixime 91.4%, doxycycline 57.9%, cotrimoxazole 29.3%, ampicillin 22.9%, ciprofloxacin 13.4%, cefuroxime 7.1%, fosfomycin

4.7%, ceftriaxone 3.6%, co-amoxiclav 3.6%, cefotaxime 3.5%, vancomycin 2.6%. **The overall antibiograms of bacterial isolates indicated that the newer quinolones are the apparent drugs of choice for empirical therapy.³**

In another study, a review of records yielded 20,180 conjunctival bacterial cultures, of which 60.1% were culture-positive. Of the culture-positive isolates, 76.6% grew gram-positive and 23.4% grew gram-negative pathogens. *Staphylococcus aureus* was the most common gram-positive pathogen isolated, and also the most commonly isolated pathogen overall. *Haemophilus influenzae* was the most common gram-negative pathogen. A significant increase in the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) was observed. The highest levels of antibiotic resistance were observed to tetracycline, erythromycin, and trimethoprim/sulfamethoxazole.⁴

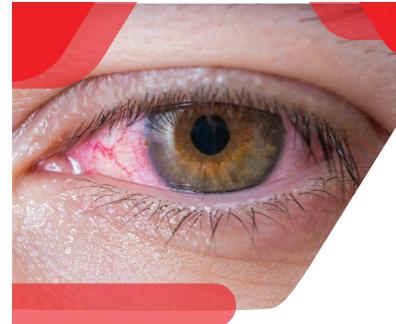
In another retrospective analysis of consecutive samples submitted for microbiological evaluation that included a total of 4417 ocular samples, 2599 (58.8%) had bacterial growth. **The rate of culture-positivity was found to be 70% in conjunctival infections and 98.7% of gram-positive isolates were susceptible to moxifloxacin.⁵**

This prospective study of 243 conjunctival cultures were done in 191 patients with chronic conjunctivitis (Table 1). Moxifloxacin showed the best in vitro activity for all isolates. The MIC₉₀ of moxifloxacin were 0.064, 0.64, and 1 for *S. aureus*-MS, *S. epidermidis*-MS, and *S. epidermidis*-MR, respectively. **Coagulase-negative staphylococci were the most frequently isolated from the conjunctiva with 58.33% of MR; and even though multiresistance was detected, their susceptibility to a fourth-generation fluoroquinolone such as moxifloxacin was preserved.⁶**

Table 1. In vitro susceptibility of coagulase-positive and -negative conjunctival isolates

Antibiotics	Susceptibility %					
	CPS-MS (n = 25)	CPS-MR (n = 4)	CNS-MS (n= 20)	CNS-MR (n = 28)	Total CPS (n = 29)	Total CNS (n = 48)
Cephalothin	68.75	100	25	100	46.43	89.66
Cefoxitin	96	0	N/E	n/e	82.76	n/e
Ciprofloxacin	70.84	100	100	70	71.43	100
Clindamycin	56.25	92	100	80	39.29	93.2
Erythromycin	41.67	84	100	60	28.58	86.3
Moxifloxacin	89.59	100	100	90	89.3	100
Oxacillin	41.67	100	0	100	0	86.3
Tobramycin	54.17	96	75	90	28.58	93.2

CPS-MS, coagulase-positive staphylococcus/methicillin susceptible; CPS-MR coagulase-positive staphylococcus/methicillin resistance; CNS-MS, coagulase-negative staphylococcus/methicillin susceptible; CNS-MR, coagulase-negative staphylococcus/methicillin resistance.



Section II

About Apdrops DX

Moxifloxacin ophthalmic solution in bacterial eye infections

Moxifloxacin hydrochloride ophthalmic solution 0.5% is the ocular formulation of moxifloxacin which is a bactericidal, concentration dependent, anti-infective. Moxifloxacin is a broad spectrum 8-methoxyfluoroquinolone which terminates bacterial growth by binding to DNA gyrase (topoisomerase II) and topoisomerase IV, essential bacterial enzymes involved in the replication, translation, repair and recombination of deoxyribonucleic acid. Affinity for both enzymes improves potency and reduces the probability of selecting resistant bacterial subpopulations. Moxifloxacin provides increased penetration into ocular tissues and fluids with improved activity against *Streptococci* and *Staphylococci* species and moderate to excellent activity against clinically relevant, gram-negative ocular pathogens.⁷

Moxifloxacin - Superior penetration

The mean corneal concentration of moxifloxacin was twice as high as ofloxacin, and the latter was twice as high as ciprofloxacin. The mean concentration of moxifloxacin in the aqueous humor was four times higher than the other antibiotics, and the mean concentrations of ciprofloxacin and ofloxacin were statistically similar. Moxifloxacin demonstrated far superior penetration into the cornea and anterior chamber of cadaver eyes compared to ciprofloxacin and ofloxacin.

Topical moxifloxacin in the treatment of bacterial conjunctivitis

Bacterial conjunctivitis is one of the most frequent forms of ocular diseases globally. It causes significant health problems, is very contagious and imposes a substantial healthcare and societal burden. Of special concern are methicillin-resistant *Staphylococcus aureus* strains which have been isolated with greater frequency over the last several years.⁸ Moxifloxacin has good activity against various Gram-positive and Gram-negative ocular isolates in vitro, and moxifloxacin 0.5%

ophthalmic solution achieves good penetration into ocular tissues in healthy volunteers and patients undergoing ocular surgery. The efficacy of moxifloxacin 0.5% ophthalmic solution in the treatment of bacterial conjunctivitis has been shown in three randomized, double-blind, multicentre trials.

1. In a trial in patients aged ≥1 year, the clinical success rate was significantly higher with moxifloxacin 0.5% ophthalmic solution than with placebo.
2. In another trial, the clinical cure rate was significantly higher with moxifloxacin 0.5% ophthalmic solution than with trimethoprim 1.0%/polymixin B 10,000 IU/mL ophthalmic solution in paediatric patients aged ≤18 years.

Moxifloxacin 0.5% ophthalmic solution was well tolerated in patients with bacterial conjunctivitis. Ocular adverse events (e.g. eye pain, eye irritation) were the most commonly reported treatment-related adverse events, with the majority being of mild severity.⁹

Moxifloxacin in nonperforated bacterial corneal ulcers

The equivalence of moxifloxacin 0.5% was compared with a combination of fortified cefazolin sodium 5% and tobramycin sulfate 1.3% eye drops in the treatment of moderate bacterial corneal ulcers. Corneal healing using 0.5% moxifloxacin monotherapy was found to be equivalent to that of combination therapy using fortified cefazolin and tobramycin in the treatment of moderate bacterial corneal ulcers.¹⁰

Moxifloxacin – Benefit over other anti-microbial agents

Compared with placebo, the use of antibacterials significantly improves clinical and microbiological remission, shortens symptom duration, and enables more effective use of healthcare resources. From a health economic perspective this is of benefit to the healthcare system and society, since fewer healthcare resources are needed and the adults affected, or the parent/caregiver of the child affected, can return to full work capacity sooner, reducing loss of productivity.

Most patients are first seen in primary care, where a 'wait-and-see' policy, lubrication eye drops and antiseptic or antibacterial treatment is given. The strategy of using topical fluoroquinolones as a last resort reflects a belief that the use of topical fluoroquinolones may enhance the development of resistance, jeopardizing future availability of antibacterial treatment for ocular infections. In fact, most cases of bacterial resistance arise as a result of systemic treatment. Thus, this concern should not be extrapolated to topical use of fluoroquinolones, which results in antibacterial concentrations at the ocular surface that can significantly exceed mutant prevention concentrations. **In addition, with agents such as topical moxifloxacin, a dual-step mutation is required for resistance to emerge. Moxifloxacin restricts the selection of resistant mutants, meaning that emergence of resistance is unlikely.**

Compared with non-fluoroquinolones, topical moxifloxacin has a higher potency and faster in vitro 'speed-to-kill'. It has also been shown that, within the fluoroquinolone class, topical moxifloxacin achieves the highest mean concentrations in conjunctival tissue, have the longest residence times and display favourable area under the concentration-time curve from time zero to 24 hours (AUC₂₄)/minimum inhibitory concentration ratio required to inhibit the growth of 90% of organisms (MIC₉₀) and thus favourable pharmacokinetic/pharmacodynamic characteristics. This can result in reduced time-to-cure and a lower number of treatment failures, leading to better disease management and a healthcare-economic benefit arising from the associated reduction in utilization of healthcare resources. The high potency and mean concentration in conjunctival tissue combined with the long residence time of topical moxifloxacin enables a dosing strategy of three times daily for 5 days.¹¹

Moxifloxacin - Better kill kinetics vs Tobramycin and Gentamycin

Bacterial conjunctivitis isolates of *S. pneumoniae* and *H. influenzae* were exposed to 1:1000 dilutions of moxifloxacin 0.5%, tobramycin 0.3%, gentamicin 0.3%, and water (control) to compare the kinetics and speed of kill of *Streptococcus pneumoniae* and *Haemophilus influenzae* (Figure 1 and Figure 2). Moxifloxacin achieved 99.9% kill (3-log reduction) at approximately 2 hours for *S. pneumoniae* and at 15 minutes for *H. influenzae*. Tobramycin and gentamicin did not achieve 3-log reduction of *S. pneumoniae* during the 180-minute study period. An increase in bacterial growth was noted for these isolates.

Gentamicin took more than 120 minutes to achieve the 3-log reduction of *H. influenzae* and tobramycin did not reach the 3-log reduction of this pathogen during the 180-minute study period.

Researchers therefore concluded that moxifloxacin killed *S. pneumoniae* and *H. influenzae* faster than tobramycin and gentamicin in vitro,

suggesting its potential clinical benefit as a first-line treatment for bacterial conjunctivitis to minimize patient symptoms and to limit the contagiousness of the disease.¹²

Moxifloxacin - Better kill kinetics vs other fluoroquinolones

Moxifloxacin's rate of kill of susceptible and resistant Gram-positive organisms were compared with *Staphylococcus aureus* and *Streptococcus pneumoniae* isolates exposed to moxifloxacin, ciprofloxacin, or ofloxacin diluted to human conjunctival concentrations achieved after instillation of one drop. Researchers concluded that moxifloxacin showed an increased speed of kill against both of the common susceptible Gram-positive conjunctival pathogens, compared with the inconsistency of killing activity of ciprofloxacin and ofloxacin. In addition, at the concentration level achieved in the conjunctiva after the instillation of one drop, moxifloxacin effectively and rapidly killed resistant Gram-positive conjunctival pathogens, while ciprofloxacin and ofloxacin had no effect against these organisms.¹³

Figure 1. Percent survivors of *Streptococcus pneumoniae* as a function of time.

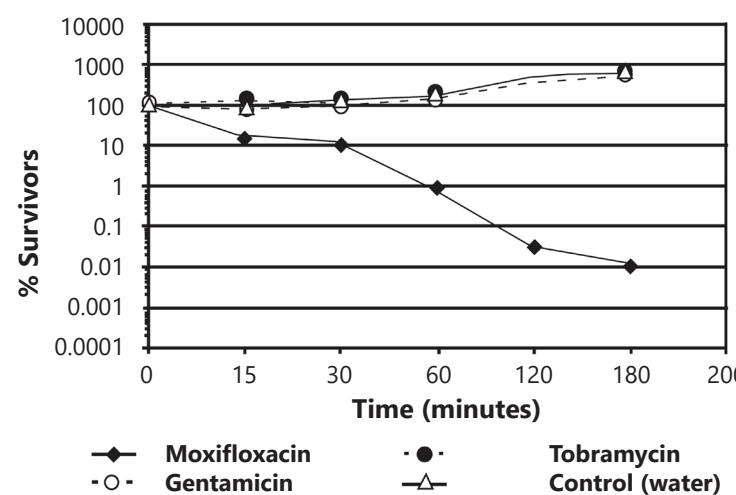
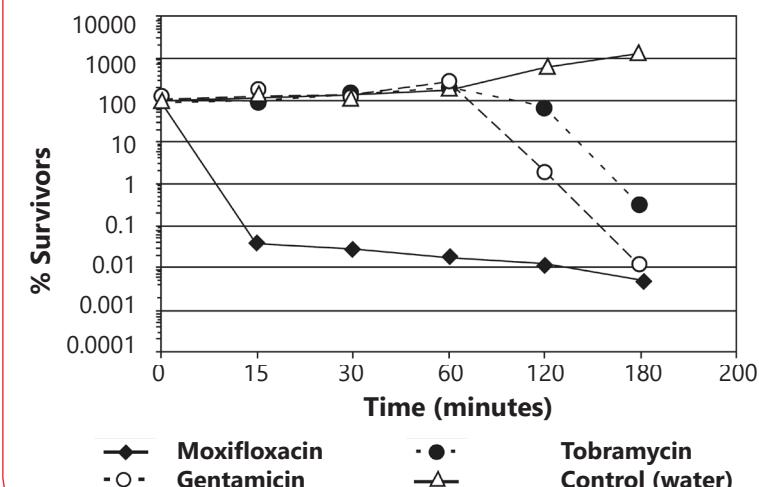


Figure 2. Percent survivors of *Haemophilus influenzae* as a function of time.



!! The strategy of not using the most effective fluoroquinolones such as topical moxifloxacin may lead to more patients with no improvement or worsening of symptoms, requiring re-intervention, additional examination and new treatment. These outcomes are defined as 'treatment failures' which cause an extra societal burden and increased costs due to the extra healthcare resources required (additional GP/specialist visits, laboratory tests, additional treatment, etc). !!



Section III

Steroids in ocular therapy

Ocular inflammation is managed by corticosteroids as they are effective in resolving postoperative inflammation and pain, increasing patient comfort, and decreasing the risk of complications. If left untreated, postoperative inflammation can also lead to suboptimal vision results or complications such as cystoid macular edema (CME).¹⁷

Focus on Dexamethasone

Dexamethasone is one of the most prescribed glucocorticoids. It is effective and safe in the treatment of a wide variety of ocular conditions, including anterior and posterior segment inflammation. The rationale for using corticosteroids to treat anterior and posterior ocular segment diseases is driven by inflammation. The potency of dexamethasone, alone or in combination with other agents, makes dexamethasone a promising option for treating several inflammatory ocular diseases.¹⁸ Innovative dexamethasone delivery systems have been designed in an attempt to achieve sustained release and targeting.¹⁹

Efficacy of fixed-dose moxifloxacin–dexamethasone combination

This study compared the aqueous humor concentrations of topically applied moxifloxacin 0.5% ophthalmic solution alone, or in combination with dexamethasone 0.1%, and correlated these concentrations with the minimum inhibitory concentrations (MICs) for common endophthalmitis-causing organisms. Sixty-eight patients undergoing routine phacoemulsification with intraocular lens implantation received either moxifloxacin 0.5% alone or moxifloxacin 0.5% combined with dexamethasone. The mean concentrations of moxifloxacin were 986.6 ng/mL in the moxifloxacin with dexamethasone group and 741.3 ng/mL in the moxifloxacin group ($P = 0.13$). Moxifloxacin concentrations of all samples exceeded the MICs for *Staphylococcus epidermidis*, *S. aureus*, and *Streptococcus pneumoniae*. All samples in the moxifloxacin with dexamethasone group and 94% in the moxifloxacin group achieved the MIC for *Enterococcus* species. For quinolone-resistant

S. aureus, the MIC was achieved in 29% in the moxifloxacin with dexamethasone group and 9% in the moxifloxacin group ($P = 0.06$). **Aqueous humor moxifloxacin concentrations were higher when topically administrated in combination with dexamethasone compared to the moxifloxacin alone.²⁰**

Moxifloxacin-dexamethasone combination eye drops for bacterial blepharitis

Treatments that offer two medications in a fixed combination have the potential to offer efficacious and safe treatment with advantages such as a regimen that is simpler than administering two separate solutions. This study evaluated the safety and efficacy of fixed-combination versus concomitant moxifloxacin 0.5% and dexamethasone 0.1% ocular solutions for the treatment of bacterial ocular inflammation and infection.

Clinical resolution occurred similarly in both groups (81.6% of eyes, fixed-dose group; 82.3% of eyes, concomitant group). Moreover, the microbiological efficacy of the treatment was also similar for both the fixed-dose group (84%) and the concomitant group (83%). Ocular symptoms and signs improved over time, with no significant differences between groups after 7 days of treatment, except the fixed-dose group had significantly more eyes with clinical resolution in eyelid erythema. Both regimens were safe and well tolerated. The fixed-dose combination of moxifloxacin, 0.5% and dexamethasone, 0.1% was therapeutically equivalent and as well tolerated as the concomitant dosage.²¹

Moxifloxacin-dexamethasone combination for topical prophylaxis

This study compared the efficacy and tolerability of a fixed-dose combination of 0.5% moxifloxacin and 0.1% dexamethasone formulation vs conventional dosing with both agents dosed separately for prophylaxis after laser-assisted in situ keratomileusis (LASIK). No ocular infection or persistent inflammation developed. Postoperatively there were no statistical differences between treatments for most parameters measured. Topical prophylaxis with 0.5% moxifloxacin and 0.1% dexamethasone eye drops was well tolerated and is therapeutically equivalent to conventional dosing with moxifloxacin and dexamethasone from individual bottles.²²

Moxifloxacin-dexamethasone combination for topical prophylaxis and reduction of inflammation after cataract surgery

This study compared the efficacy and safety of a combined 0.5% moxifloxacin and 0.1% dexamethasone formulation versus conventional dosing with 0.5% concomitant moxifloxacin and 0.1% dexamethasone for the prevention of infection and control of inflammation after cataract surgery. Treatment with the combined moxifloxacin/dexamethasone eye drops was as effective as conventional treatment in preventing infection and controlling inflammation after phacoemulsification and IOL implantation.²³



Section IV

Cyclodextrins: Enhancing topical delivery of corticosteroids

Corticosteroids in ophthalmology

The most common use of corticosteroids in eye drops is for inflammation following eye surgery, such as cataract surgery and corneal operations. Corticosteroids are generally lipophilic and dissolve very poorly in water but topically applied drugs must be, at least to some degree, soluble in the aqueous tear fluid. They must also be somewhat lipid soluble in order to penetrate the lipophilic corneal epithelium, through the corneal stroma and the lipophilic endothelium into the aqueous humour. In other words, for successful formulation in an aqueous eye drop solution, a drug must be both water-soluble (i.e. hydrophilic) and lipid-soluble (i.e. hydrophobic).

Corticosteroids are generally not effective in the posterior segment of the eye and, therefore, systemic corticosteroids are needed to fight inflammatory disease in this area.

Various researchers have studied the penetration of topically applied ocular steroids into the anterior chamber of the human eye. They found that of the commercially available formulations containing 0.1% dexamethasone alcohol suspension gave a considerably lower concentration despite being seven times more potent than prednisolone. The dexamethasone concentration obtained in the aqueous humour corresponded to about 60 ng/mL of prednisolone. The most effective corticosteroid eye drops available today give aqueous humour concentration of less than 100 ng/mL (prednisolone equivalents).

The continuous secretion of tear fluid adds to this difficulty by limiting the contact time of topically applied drugs with the eye surface, which again reduces their ocular bioavailability, especially after application in low viscosity aqueous eye drop solutions. Consequently, less than 5% of a topically applied drug is absorbed through the cornea into the eye. Common adjuvants to aqueous eye drop formulations can enhance ocular bioavailability of steroids by reducing the barrier function of, for example, the cornea (e.g. benzalkonium chloride and other surfactants) or by increasing the contact time of the drug with the eye surface (e.g. viscosity enhancers such as water-soluble polymers).

Specialized ocular delivery systems such as hydrogels, microemulsions, solid inserts and liposomes have also been designed in order to enhance bioavailability of topically applied ophthalmic drugs. However, these have never gained much popularity, due to both their side effects (such as blurred vision and local irritation) and their instability (i.e. limited shelf-life).

This bioavailability can be improved through the use of cyclodextrin formulation, where a single drop topical application gives aqueous humour concentration of about 140 ng/mL (prednisolone equivalents) and also extends its duration in the eye.

Cyclodextrins

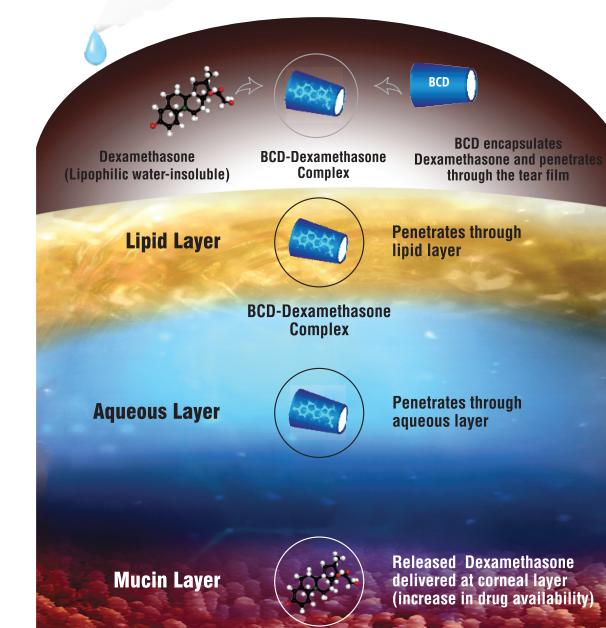
Cyclodextrins are novel, chemically stable adjuvants that enhance ocular bioavailability of ophthalmic drugs without affecting the barrier function of the eye or increasing the viscosity of the aqueous eye drop formulation. They are cylindrical oligosaccharides with a lipophilic central cavity and hydrophilic outer surface that can form water-soluble complexes with lipophilic drugs, which 'hide' in the cavity. Cyclodextrins can be used to form aqueous eye drop solutions with lipophilic drugs, such as steroids and some carbonic anhydrase inhibitors.

The cyclodextrins increase the water solubility of the drug, enhance drug absorption into the eye, improve aqueous stability and reduce local irritation. Cyclodextrins are useful excipients in eye drop formulations of various drugs, including steroids of any kind, carbonic anhydrase inhibitors, pilocarpine, cyclosporins, etc.

Their use in ophthalmology has already begun and is likely to expand the selection of drugs available as eye drops. Cyclodextrins have been used to formulate eye drops containing corticosteroids, such as dexamethasone, with levels of concentration and ocular absorption which, according to human and animal studies, are many times those seen with presently available formulations.

Cyclodextrin-based dexamethasone eye drops are well tolerated in the eye and seem to provide a higher degree of bioavailability

Ocular penetration is enhanced by Beta-cyclodextrin (BCD)²⁴



and clinical efficiency than the steroid eye drop formulations presently available. Such formulations offer the possibility of once per day application of corticosteroid eye drops after eye surgery, and more intensive topical steroid treatment in severe inflammation.

While cyclodextrins have been known for more than a century, their use in ophthalmology is just starting. Cyclodextrins are useful excipients in eye drop formulations for a variety of lipophilic drugs. They will facilitate eye drop formulations for drugs that otherwise might not be available for topical use, while improving absorption and stability and decreasing local irritation.²⁴

Cyclodextrins and topical drug delivery to the anterior and posterior segments of the eye

It is generally believed that it is virtually impossible to obtain therapeutic drug concentrations in the posterior segment of the eye after topical application of aqueous, low viscosity eye drops. Through proper analysis of the drug permeation barriers and application of well-known pharmaceutical excipients, aqueous eye drops are designed that can deliver lipophilic drugs to the posterior segment as well as how such eye drops can maintain high drug concentrations in the anterior segment. Studies in rabbits and clinical evaluations in humans using dexamethasone show that the eye drops deliver significant amounts of drugs to both the posterior segment and anterior segment of the eye.²⁵

Cyclodextrin complexation of a drug molecule changes the physicochemical properties of the drug, such as its aqueous solubility and chemical stability. Since the cyclodextrin molecule is hydrophilic on the outside, the complex formation usually increases the water-solubility of lipophilic water-insoluble drugs. Thus, it has been possible through cyclodextrin complexation to formulate lipophilic water-insoluble steroids as aqueous eye drop solutions.

Furthermore, the chemical stability of the drug molecule is enhanced by the inclusion complexation. This increases the shelf-life of the aqueous eye drop formulation. The effects of cyclodextrins on drug solubility, permeability, chemical stability and delivery through biological membranes have been investigated by a number of research groups. Their studies show that hydrophilic cyclodextrins act as true carriers by keeping the lipophilic water-insoluble drug molecules in solution and delivering them to the membrane surface where they partition from the cyclodextrin cavity into the lipophilic membrane. The relatively lipophilic membrane has low affinity for the large hydrophilic cyclodextrin molecules or the hydrophilic drug/cyclodextrin complexes, which thus remain in the aqueous skin exterior, e.g. the aqueous tear fluid.

Conventional penetration enhancers, such as benzalkonium chloride, disrupt the ophthalmic barrier, whereas hydrophilic cyclodextrins enhance drug penetration into the eye by carrying the lipophilic water-insoluble drug molecules through the aqueous mucin layer and thereby increasing drug availability at the lipophilic eye surface.

In vivo observations

Dexamethasone/2-hydroxypropyl- β -cyclodextrin eye drops give a significantly higher concentration of dexamethasone in the aqueous humour than did dexamethasone (0.1% w/v) alcohol suspension, even though the difference in concentration in the aqueous humour was less than the 13-fold difference in the concentration of dexamethasone in the eye drop. Four hours after the application of dexamethasone (0.1% w/v) alcohol suspension, the concentration of dexamethasone in the aqueous humour was essentially zero, whereas the cyclodextrin-dexamethasone solution gave about 100 ng/mL. The cyclodextrin-dexamethasone eye drop solution was well tolerated and no irritation was seen on clinical examination.

The ocular absorption of dexamethasone eye drops containing 2-hydroxypropyl- β -cyclodextrin was also tested in human patients and compared with 0.1% dexamethasone alcohol suspension. The concentration of dexamethasone in the aqueous humour was significantly higher ($P < 0.001$) and the area under the curve was 2.6 times higher with the 0.32% cyclodextrin-dexamethasone eye drop solution than with dexamethasone (0.1% w/v) alcohol suspension. The peak concentration of dexamethasone did not increase when the dexamethasone concentration in the aqueous cyclodextrin containing eye drops was increased from 0.32 to 0.67% (w/v). Concentration values obtained 9 hr after administration show that the duration of activity was increased (Table 3).

Researchers conclude that cyclodextrins make it possible to formulate lipophilic drugs in aqueous eye drop solutions and increase the drug concentration and bioavailability that offer more effective and less frequent treatment schedules for patients with ocular inflammation.

Table 3. Adjusted mean peak concentration (\pm standard error of the mean) of dexamethasone and prednisolone acetate, and the concentration at + 9hrs, in aqueous humour of human volunteers after topical administration. Concentrations are adjusted for potency of prednisolone, which is a seven-fold weaker steroid than dexamethasone.

Eye drop solution	Mean peak concentration (ng/ml)	Concentration at + 9hrs (ng/mL)
Dexamethasone 0.32%	141 \pm 36	0
Dexamethasone 0.67%	130 \pm 50	18 \pm 5
Dexamethasone (0.1% w/v) alcohol suspension	60 \pm 21	0
Prednisolone acetate 1%	96 \pm 19	-



Section V

Apdrops DX - Clinical pharmacological profile

Composition

Each ml contains:

Moxifloxacin Hydrochloride BP	5.0 mg
Dexamethasone Sodium Phosphate BP	1.0 mg
Benzalkonium Chloride NF (as preservative)	0.01% w/v
Sterile aqueous vehicle	q.s.

List of excipients - Boric Acid BP, Borax (Sodium Borate) BP, Sodium Chloride BP, Hydroxypropylbetadex BP, Bezalkonium Chloride USPNF, Water for Injections BP.

Therapeutic indications - Apdrops DX is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection of a risk of bacterial ocular infection coexists.

Posology and method of administration - Instill one drop in the affected eye 3 times a day for 7 days.

Contraindications - Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and in many other viral diseases of the conjunctiva and cornea. Mycobacterial infections of the eye. Fungal diseases of ocular structures. Hypersensitivity to any of the components of the medication.

Special warning and precautions for use - Not for injection into eye. Prolonged use of steroids may result in glaucoma. If this product is used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and unco-operative patients. In those diseases, causing thinning of the cornea or sclera, perforations have been known

to occur with the use of topical steroids. The possibility of fungal infections of the cornea should be considered after long term steroids dosing. If super infection occurs, appropriate therapy should be initiated.

Interactions with other medicinal products and other forms of interactions

- Drug-drug interaction studies have not been conducted with Moxifloxacin Hydrochloride ophthalmic solution. In vitro studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Pregnancy and lactation - Pregnancy: Apdrops DX should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. Lactation: It is not known whether topical administration of the combination would result in sufficient systemic absorption to produce detectable quantities in human milk. Caution should be exercised when the combination is administered to nursing women.

Effects on ability to drive and use machine - As with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Undesirable effects - Adverse effects have occurred with steroid/anti-infective combination drugs, which can be attributed to the steroid component, the anti-infective component, or the combination. The most frequently reported ocular adverse events with Moxifloxacin when used alone were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, sub-conjunctival haemorrhage and tearing. These events occurred in approximately 1 to 6% of patients. Non-ocular adverse events reported at rate of 1 to 4% were fever, increased cough, infection, otitis media, pharyngitis, rash and rhinitis. The adverse reactions reported due to the steroid component when used alone are elevation of intraocular pressure (IOP) with possible development of glaucoma and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

Storage - Store below 30°C.

Presentation - A carton containing 5 ml LDPE vial containing 5 ml solution along with pack insert.



Section VI

Apdrops DX - Synergy for treating intra-ocular inflammation/infections

PARAMETERS	APDROPS DX	TOBRAMYCIN WITH DEXAMETHASONE
Penetration	Higher	Not sufficient
Killing rates for susceptible organisms	99% killed at 120 min - achieved	99% kill at 180 min - not achieved
Resolution of infection	Within 3 days	Within 8 days
Toxicity	No toxic profile	Mild toxicity evidence detected
Potential combination advantage	Enhances ocular penetration and reduce eye irritation	Not known



Section VII

Key Take Home Message

- ✓ Acute bacterial conjunctivitis treatment includes measures to prevent spread, and giving topical antibiotics (such as a fluoroquinolone for bacterial causes excluding gonococcal and chlamydial).
- ✓ Apdrops-DX is used to treat inflammation and infection of the eye. It is indicated in the following eye conditions:
 - ◊ Conjunctivitis.
 - ◊ Bacterial blepharitis.
 - ◊ As an antibiotic and anti-inflammatory prophylaxis post-cataract & other ocular surgeries.
- ✓ Moxifloxacin killed *S. pneumoniae* and *H. influenzae* faster than tobramycin and gentamicin in vitro, suggesting its potential clinical benefit as a first-line treatment for bacterial conjunctivitis
- ✓ Moxifloxacin - Dexamethasone combination allows better penetration of moxifloxacin through the ocular tissues. Such synergy of penetration is not known with Tobramycin - Dexamethasone combination.
- ✓ Beta-cyclodextrin (BCD) – a unique carrier system in Apdrops-DX improves the drug penetration, thus improving the efficacy. The fixed drug combination reduces the number of application of drugs to be administrated per day, thereby increasing the patient compliance and adherence.

PARAMETERS	APDROPS DX	OFLOXACIN, TETRYZOLINE, PREDNISOLONE, BAK
Penetration	Higher	Not sufficient
MIC	Lowest MIC compared to Ofloxacin	Higher MIC compared to Moxifloxacin
Killing rates for susceptible organisms	Superior to Moxifloxacin	Inferior to Moxifloxacin
Potential combination advantage	Enhances ocular penetration and reduces eye irritation	Not known

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