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ENHANCING OCULAR THERAPEUTICS: A COMPREHENSIVE REVIEW

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ABSTRACT

Targeting drugs to the ocular surface remains challenging owing to the unique and intricate anatomy of the human eye. Effective drug entry into the desired site is obstructed by ocular protective structures, including the blood-aqueous and blood-retinal barriers. Although ointments, drops, and suspensions are easy to apply and therefore favoured by patients, their therapeutic outcome is limited because most of the dose is quickly cleared from the eye surface.

For decades, formulation scientists have explored alternative delivery systems that can address the shortcomings of conventional dosage forms. Among these, in-situ gelling systems, also known as gel forming solutions, offer a practical option because they undergo a fluid-to-gel transition triggered by shifts in pH, temperature, or ionic concentration. Once instilled into the eye, the solution converts into a gel that prolongs corneal contact and reduces drainage of the formulation. Fluoroquinolones, an expanding family of broad-spectrum antibacterials, are active against a wide range of gram-negative and anaerobic organisms that cause ocular infections. Owing to clinical evidence showing efficacy comparable to combination regimens across several ocular infections, this class has gained widespread use in ophthalmology.

The present review compiles current information on ocular gel forming solutions, covering the mechanism behind the sol-to-gel transition, supporting clinical and laboratory studies, and key evaluation parameters. The use of fluoroquinolones, when delivered through gel forming solution platforms for managing ocular infections, is also examined.

Keywords: Gel forming Solution; Sustained delivery; Ocular infections; Keratitis; Fluoroquinolones

1. INTRODUCTION

Common ocular infections

Any structure of the eye, from the eyelid to the retina, is vulnerable to bacterial invasion, and severe infections can ultimately progress to vision loss. According to the World Health Organization (WHO), untreated bacterial infections of this delicate organ remain among the global contributors to preventable blindness.

Among the bacterial pathogens commonly implicated in ocular infections are S. aureus, P. aeruginosa, S. pneumoniae, Neisseria, and Chlamydia species, in addition to several others.

Conjunctivitis, keratitis, eye stye, uveitis, corneal ulcers, blepharitis, dacryocystitis, and endophthalmitis are some of the frequently encountered ocular infections[1].

Ocular infections may be triggered by bacteria, viruses, or fungi, and the spectrum is broad. Frequently reported conditions worldwide include Conjunctivitis, Keratitis, Eye stye, Corneal ulcers, Blepharitis, Uveitis, Dacryocystitis, Endophthalmitis, Herpes Zoster ophthalmicus, Optic neuritis, and Chorioretinitis, among others.

Conjunctivitis

One of the most widely encountered eye conditions globally is conjunctivitis. It can arise from a range of agents, including bacteria, viruses, fungi, allergic spores, parasites, and other triggers, although bacterial and viral forms dominate in worldwide prevalence[2]. The disorder presents with conjunctival swelling, inflammation, ocular pain, and discharge[3], and is popularly known as “pink eye” or “madras eye”. Watering, redness, and irritation are typical clinical features[4]. The various forms of conjunctivitis together with their causative organisms are summarised in Table 1.

Table 1: Different forms of conjunctivitis along with causative organism

S. No.	Type of conjunctivitis	Causative organism
1.	Bacterial conjunctivitis	Staphylococcus aureus, Streptococcus pneumoniae
2.	Viral conjunctivitis	Herpes simplex, Varicella zoster, Enterovirus, Adenovirus
3.	Allergic conjunctivitis	Not caused by any microbe, caused by pollen, dust, and animal dander
4.	Fungal conjunctivitis	Candida, Fusarium and Aspergillus
5.	Parasitic conjunctivitis	Acanthamoeba
6.	Chemical conjunctivitis	Caused by smoke, chlorine used in swimming pools and other chemicals
7.	Neonatal conjunctivitis	Chlamydia trachomatis, Neisseria gonorrhoeae

Bacterial conjunctivitis is generally treated with fluoroquinolone-class agents including ofloxacin and ciprofloxacin[5]. The viral form lacks a dedicated treatment regimen; however, cold compresses and artificial tears are commonly advised for symptomatic relief. For the allergic variant, antihistamines are the typical choice[6].

Keratitis

Inflammation of the cornea, frequently arising from contact lens-associated infection or ocular trauma, is termed keratitis and is also called "corneal inflammation". When left without treatment, the condition can progress to blindness, making it a leading contributor to vision loss globally[7]. The principal pathogens implicated in keratitis include viruses, bacteria, fungi, and parasites[8] with Staphylococcus aureus and Pseudomonas Aeruginosa being the predominant bacterial causes. Patients typically experience blurred vision, redness, itching, and watery discharge.

Antibacterial management of keratitis commonly relies on fluoroquinolone antibiotics, including levofloxacin, gatifloxacin, and moxifloxacin[9]

Patients diagnosed with keratitis are routinely advised to discontinue contact lens use, as contaminated lenses can exacerbate the ocular condition.

Eye stye

The eyelids contain sebaceous glands that lubricate the ocular surface. Bacterial or microbial infection of these glands leads to their blockage, producing a small swelling on the upper or lower eyelid, a condition also referred to as hordeolum, Jawad and Taghreed[10]. Poor personal hygiene and unhygienic surroundings are recognised triggers.

The protruded swelling causes considerable discomfort and gives a gritty sensation in the eye, accompanied by redness, swelling, and pain. Although no dedicated treatment exists for eye stye, warm compresses together with topical ointments are advised for rapid relief of pain[11].

Corneal ulcers

Corneal ulcer is an ocular disease marked by inflammation of the eye's outermost layer[12]. It poses a serious threat to vision and ranks among the chief causes of blindness in developing nation[13]. Viral, bacterial, and fungal pathogens are the principal contributors to corneal ulcer development, while allergic reactions or endogenous factors may occasionally be involved. Corticosteroid use is another significant factor, since these agents promote fungal proliferation in the corneal region[14]

Blepharitis

Inflammation of the eyelid margins, known as blepharitis, frequently coexists with other ocular conditions including conjunctivitis, keratitis, and rosacea[15]. The condition affects individuals across all age groups and presents with burning, irritation, itching, blurred vision, watering, and photosensitivity[16]. Since neglect of eyelid hygiene contributes substantially to the development of blepharitis, maintaining cleanliness of the lid region is essential.

Short-term use of cortisone-containing ointments and creams is recommended for managing the condition[17].

Uveitis

Inflammation of the middle layer of the eye, the uveal tract, is referred to as uveitis[18]. Anatomically, the condition is classified as anterior or posterior; the anterior form affects the iris or ciliary body, whereas the posterior form involves the retina and choroid. Contributing factors include age, sex, genetic predisposition, and social habits. Histopathological classification further divides uveitis into granulomatous and non-granulomatous types.

Patients with uveitis typically report floaters, ocular pain, photosensitivity, and, in advanced stages, visual loss[19]. Diagnostic assessment is carried out using ophthalmoscopy and tonometry. Treatment generally involves anti-inflammatory therapy combined with steroid injections[20].

Dacryocystitis

Dacryocystitis is an obstructive inflammatory disorder affecting the lacrimal sac. Blockage of the sac results in the build-up of tear fluid that subsequently triggers inflammation. Common clinical manifestations include pus discharge, redness, swelling, and pain[21]. Antibiotic therapy with ciprofloxacin, clindamycin, amoxicillin, or trimethoprim, generally given orally or intravenously, is used to manage the condition[22]

Endophthalmitis

Endophthalmitis refers to bacterial or fungal infection of the inner ocular structures, particularly the vitreous and aqueous humor. The condition may stem from exogenous or endogenous causes[23], with trauma and surgery being notable precipitating factors. It is most often observed following cataract surgery. The vitreous humor is more prone to endophthalmitis than the aqueous humor, since the latter has a high turnover rate while the former does not regenerate readily[24].

Herpes Zoster ophthalmicus

An ocular infection brought about by varicella, the same agent that causes chickenpox in humans, is termed herpes zoster ophthalmicus. It typically involves the region around the trigeminal nerve and is among the more frequently encountered herpes zoster manifestations[25]. The condition predominantly affects elderly individuals and those with compromised immunity. Clinical features include ocular inflammation, pain around the trigeminal nerve distribution, and progressive vision loss. First-line therapy relies on antiviral agents such as acyclovir, famciclovir, and others[26]. Vaccination is also a valuable preventive measure for this condition[27]

Optic neuritis

Optic neuritis ranks among the most frequent ophthalmic neuropathies in young adults; it involves demyelination of the optic nerve that culminates in nerve inflammation[28]. Diagnosis can be established through MRI, visual assessment, and CSF analysis[29]. The condition serves as one of the most common clinical presentations in approximately 20% of multiple sclerosis (MS) cases[30]. Corticosteroids are widely employed to restore vision, though prolonged use carries adverse effects[31].

2. ANATOMY AND PHYSIOLOGY OF HUMAN EYE

Anatomically, the human eye is a spherical, ball-shaped organ with a diameter close to 23 mm. It contains three principal chambers, namely the anterior, posterior, and tear chambers. The posterior chamber houses the retina, choroid, sclera, and vitreous humor, while the anterior segment includes the cornea, ciliary body, iris, and aqueous humour, Anterior chamber[32]

Cornea

Situated in the anterior part of the eye, the cornea forms the outermost layer and is approximately 0.5mm thick. It generally appears as the transparent, visible bulge of the eye. Structurally, five layers comprise the cornea, namely the stroma, endothelium, Bowman's membrane, corneal epithelium, and Descemet's membrane. Lacking blood vessels, the cornea derives its essential nutrients from capillaries terminating along its periphery[33]. Its primary role is to refract and focus light entering the eye so that the image is projected onto the retina[34]

Ciliary body

Roughly triangular in shape, the ciliary body comprises ciliary muscles together with their processes. Its bilayered covering, known as the ciliary epithelium, is the source of aqueous humor production[35]. The ciliary muscles contribute significantly to lens accommodation, with their contraction and relaxation regulating the curvature of the lens.

Iris

The iris is composed of pigmented epithelial cells. Pupillary constriction and dilation are termed miosis and mydriasis, respectively. Positioned behind the cornea but in front of the lens[36], the iris regulates pupil size, thereby adjusting the quantity of light entering the eye. Its colour varies among individuals and may be blue, brown, grey, green, or hazel.

Aqueous humour

Filling the outer compartment of the eye, the aqueous humour is a jelly-like, slightly alkaline fluid owing to traces of sodium and chloride ions. Located between the cornea and the lens, it serves both nutritive and protective functions. Continuous secretion of this fluid is carried out by the ciliary processes of the ciliary body. Drainage of the aqueous humour from the anterior chamber occurs through Schemms' canal, from where it enters the venous circulation[37].

Posterior chamber

Retina

Positioned at the posterior aspect of the human eye, the retina is responsible for constructing the image of an object after light has traversed the other ocular structures. Because of the photosensitive cells it contains, the retina is highly light sensitive.

Choroid

Sandwiched between the sclera and the retina, the choroid is built from several layers including Bruch's membrane, vessel layers, and choriocapillaris[38]. It is brown in colour and densely vascularised,

harbouring a large network of blood vessels.

Vitreous humour

Occupying the space between the retina and lens, the vitreous humour is made up of collagen fibrils and hyaluronic acids. This jelly-like fluid accounts for roughly 80% of the human eye's volume and is bounded by a fine envelope termed the hyaloid membrane.

Sclera

The white outermost spherical layer of the eye, called the sclera, is composed of collagen along with elastic fibres. It is comparatively thin at the anterior aspect and thicker towards the posterior side[39]. Its principal function is to provide protection to the internal ocular structures. The sclera reaches a maximum thickness of approximately 1 mm.

3. BARRIERS IN OCULAR DRUG DELIVERY

Effective drug delivery to the ocular surface is impeded by several biological barriers, which are broadly grouped into static, dynamic, and metabolic categories.

Static barriers encountered during ocular medication transport include the blood-aqueous barrier, blood-retinal barrier, corneal barrier, and retinal pigmented epithelium (RPE). Among the corneal layers, the epithelium represents the narrowest one, and due to its strongly lipophilic character, it restricts the permeation of hydrophilic drugs. Drug entry into the retina is similarly limited by the RPE[40]

Another major obstruction to ocular drug distribution is the blood-aqueous barrier, formed by tight junction cells that restrict the passage of hydrophilic molecules. Efflux transporters located within this barrier continually expel substances from the aqueous humour, making drug retention in this region difficult. In a comparable manner, the blood-retinal barrier prevents the diffusion of large molecules across it.

The tear film represents one form of dynamic barrier; it rapidly removes drug from the ocular surface, thereby shortening contact time. Additional contributors to the rapid clearance of medication from the ocular surface include blinking, lacrimal drainage, aqueous humour turnover, and choroidal blood flow[41]

4. UNDERSTANDING THE COMPLEXITIES OF OCULAR DRUG ABSORPTION MECHANISMS

Among ocular drug delivery options, the topical route via eye drops remains the most preferred for reaching the cul-de-sac of the eye. The availability of the drug within the tear film depends on three principal mechanisms, namely diffusion, erosion, and dissolution. Drug absorption at the ocular surface is broadly classified into corneal and non-corneal routes[42]. Because of the intricate anatomical layering of the cornea, drugs intended for corneal permeation must possess adequate solubility in both aqueous and lipid environments, with the stroma, epithelium, and endothelium acting as principal barriers. The non-corneal pathway, in which the drug crosses the sclera and conjunctiva before reaching the tissues, is comparatively inefficient and applies mainly to drugs with poor corneal

permeability; the corneal route, by contrast, involves drug movement from the cornea into the intraocular tissues by way of the aqueous humour.

5. OCULAR DRUG DELIVERY SYSTEM (ODDS)

Reaching the desired ocular site with adequate drug concentration is challenging on account of the distinctive structural complexity of the eye. The numerous ocular barriers outlined in earlier sections restrict drug entry into the target tissues, with the result that therapeutic efficacy is often suboptimal[43]. Drops, ointments, and suspensions are conventional dosage forms widely used for ocular drug delivery because they are easy to apply and acceptable to patients[44]. Nevertheless, the therapeutic outcome of these formulations remains limited, largely because the dose is rapidly cleared from the ocular surface[45].

Several approaches have been devised to address the issue of rapid drug clearance from the ocular surface, including the use of polymers to achieve sustained release and prolonged drug action. Formulation parameters such as viscosity and particle size are tuned so that the dose is delivered gradually over a longer duration, while other approaches aim to circumvent the external ocular barriers and place the therapeutic agent directly into the anterior or posterior segment of the eye.

Designing an effective ocular drug delivery system depends on a sound appreciation of the eye's intricate anatomy and physiology, the physicochemical attributes of the drug, and the disease for which the formulation is being developed[46]. Optimising each of these aspects can lead to a therapeutic regimen with improved performance. A further objective for formulation scientists is to design a dosage form that retains the drug at the intended site for the required duration, reduces unwanted systemic side effects, and enhances patient compliance while remaining easy to administer without specialised assistance[47,48].

6. MODES OF OCULAR DRUG ADMINISTRATION

Drug may be delivered to the eye through a variety of routes, with the choice of route guided primarily by the intended target site or tissue[49]. Depending on the target tissue, the available ocular delivery routes include topical, intracameral, intravitreal, subconjunctival, subretinal, retrobulbar, and systemic administration[50].

Topical route

Eye drops represent the typical means of topical ocular drug administration, which is among the most frequently used routes. Owing to its non-invasive nature and good patient acceptance, this route accounts for approximately 95% of marketed ocular products. Its main limitation, however, is the short contact time, since a large portion of the instilled dose is washed away with tear fluid. Newer dosage forms such as in-situ gels and implants have therefore been developed to extend the time the drug remains in contact with the ocular surface.

Intravitreal route

Drug is administered through this route by direct injection into the vitreous humour, which provides immediate access to the

retina and vitreous humour and improves therapeutic efficacy[51]. Reaching the choroid, however, is hampered by the retinal pigmented epithelium (RPE), which restricts the movement of large molecules and permits only small molecules to diffuse rapidly across it. As the procedure is invasive, local anaesthetics are commonly employed.

Subconjunctival route

Direct injection under the conjunctiva allows the drug to circumvent the epithelium, which is the principal barrier to ocular delivery. This route proves useful when high drug levels are required at the ocular surface. An injection placed beneath the eyeball is termed epibulbar, whereas one delivered under the conjunctival lining is referred to as sub-palpebral.

Intracameral route

This route is mainly employed to deliver drugs to the anterior segment of the eye and helps overcome multiple ocular delivery barriers. Several agents administered intracamerally have demonstrated effective disease management, owing to the enhanced drug concentration achieved within the target tissue[52]

Retrobulbar route

The retrobulbar route entails injecting the drug directly into the retrobulbar space. For managing certain fungal infections, this approach has shown advantages over intravenous administration.

Systemic administration

Systemic ocular drug delivery involves direct introduction of the drug into the bloodstream, generally through intravenous administration. A notable disadvantage of this route is that it demands precise dosing and skilled personnel, since once the drug enters circulation, controlling the therapeutic action becomes difficult, particularly when the dose is large.

7. NOVEL APPROACHES FOR TARGETED OCULAR DRUG DELIVERY

Numerous developments in ODDS have been made to enhance ocular drug absorption, surmount the barriers that limit drug entry into the eye, and achieve sustained release[53]. The following are some of the recently introduced ocular drug delivery systems:

Nanoparticles built from biodegradable polymers such as PLGA are emerging delivery systems that enable controlled release of the encapsulated drug[54]

Liposomes represent another recent development, in which phospholipid vesicles can carry both hydrophilic and lipophilic drugs, thereby facilitating their transport to the lipophilic ocular surface[55]

Dendrimers, which are highly branched architectures, can entrap drug molecules within their framework and improve overall drug bioavailability.

Microneedles are a newer category of dosage forms that create microchannels on the ocular surface to promote drug penetration. Dissolving microneedles offer an additional benefit over solid microneedles, since they dissolve after releasing the drug and consequently do not pose a risk of ocular toxicity[56]

Hydrogels are formed from hydrophilic polymers capable of holding considerable amounts of water and releasing the entrapped drug in a sustained fashion.

Different categories of hydrogel systems exist, including thermos-responsive and pH-responsive variants.

Drug-loaded or impregnated contact lenses constitute a dosage form capable of releasing drug molecules over an extended period. Nanoparticle coating of contact lenses can also be applied to provide finer control over drug release[57].

Implants represent another notable advance in ODDS; they are positioned within the target tissue through minor surgery and can release the drug for months. They may be fabricated from biodegradable or non-biodegradable polymers; the biodegradable type degrades within the ocular tissue and thus requires no removal, whereas non-biodegradable implants must be removed surgically.

Gene and RNA-based therapies, which make use of viral vectors and mRNA molecules, offer effective approaches and are particularly valuable for the management of genetic ocular disorders[58].

A further important advance in ODDS, intended to address the barriers and limitations described above, is the in-situ gelling system or gel forming solution, which switches rapidly from sol to gel in response to triggers such as changes in temperature, pH, or ionic activation[59]

These innovative ocular drug delivery system regimens are reshaping the practice of ocular therapy and offer greater convenience together with better efficacy than standard conventional dosage forms[60].

8. CONCLUSION

Progress in ocular drug delivery using gel forming solutions for managing ocular infections holds considerable promise. Such formulations deliver the drug over an extended duration, retain it well at the target site, and enhance patient compliance because they need to be applied less frequently.

Recent progress in polymer science has further established the compatibility of gel forming solutions with ocular tissues and their ability to transport a range of antimicrobial agents to the intended targets. Despite these advantages, the principal hurdles for these dosage forms remain the upkeep of sterility and the difficulty of scaling production to commercial levels. Investigators continue to evaluate a variety of gel forming polymers for their performance during the sol-to-gel transition; nonetheless, in-vivo investigations are still needed to confirm the safety, efficacy, and patient acceptability of these systems in the wider population. Overall, ocular gel forming solutions represent a promising component of the ocular drug delivery system.

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