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ENHANCING OCULAR THERAPEUTICS: A COMPREHENSIVE REVIEW

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ABSTRACT

Human eye has peculiar complex anatomical characteristics which makes it difficult to deliver the therapeutic agent directly to the targeted site in the ocular surface. Various ocular barriers such as blood-retinal barrier, blood-aqueous barrier hinders the delivery of the drug to desired site. Various conventional ocular dosage forms such as drops, ointments, suspensions offer patient compliance due to ease of administration but are unable to produce adequate therapeutic effect due to the washout of the drug from the ocular surface.

Researchers have been working hard over decades to develop such novel system/ formulations that can overcome the limitations seen with conventional dosage forms. In-situ gelling systems/ gel forming solution solve the drawbacks of traditional dosage forms like eye drops and suspensions simply because they show sol-gel transformation by change in pH, temperature, or ionic strength. Because they can form gel following ocular instillation, they extend the corneal residence period and restrict the drainage of the formulation. A growing class of broad-spectrum antibacterials known as fluoroquinolones combats a variety of gram-negative and anaerobic bacteria that cause infections in the eyes. Since these antibacterials have been demonstrated to be equally effective as combination therapying treating a variety of ocular infections, they have become increasingly well-liked in the area of ophthalmology.

In this review article, comprehensive information on ocular gel forming solution along with mechanism of sol to gel transition, clinical trials, various studies, and evaluation parameters have been discussed. Also, it discusses the role of fluoroquinolones in the treatment of ocular infections when formulated as gel forming solutions.

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

1. INTRODUCTION

Common ocular infections

Bacterial infections can easily infect any part of the eye from eyelids to the retina, and in case of major bacterial infections lead to blindness. Bacterial infections are common cause of blindness all over the world if left untreated as eyes are the most delicate organ of the human eye, as reported by World Health Organization (WHO).

Various bacteria responsible for causing ocular infections include S. aureus, P. aeruginosa, S. pneumoniae, Neisseria, Chlamydia species and many more.

Examples of common ocular infections are- conjunctivitis, keratitis, eye stye, uveitis, corneal ulcers, blepharitis, dacryocystitis, and endophthalmitis[1].

There are a range of ocular infections mainly caused bacteria, virus, and fungi. Most commonly reported ocular infections in the world includes Conjunctivitis, Keratitis, Eye stye, Corneal ulcers, Blepharitis, Uveitis, Dacryocystitis, Endophthalmitis, Herpes Zoster ophthalmicus, Optic neuritis, Chorioretinitis, and many more.

Conjunctivitis

Conjunctivitis is one of the most ocular conditions prevailing in the world. Various types of microorganisms can be responsible for conjunctivitis and these microorganisms include bacteria, virus, fungi, allergic spores, parasites and others out of which bacterial and viral conjunctivitis are the most common types prevailing in the world[2]. In this condition, there is swelling and inflammation of the conjunctival tissue leading to pain and ocular discharge[3] Conjunctivitis is commonly referred by the name “pink eye” or “madras eye”. Signs and symptoms of Conjunctivitis include watering, redness, irritation[4]. Table 1 lists the different forms of conjunctivitis and the causing organism.

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

Antibiotics of fluoroquinolone category such as ofloxacin and ciprofloxacin are used in the management of bacterial conjunctivitis[5]. No specific treatment and management regimen are not available for viral conjunctivitis but cold compress and artificial tears are recommended for relief. Antihistamines are used for the management of allergic conjunctivitis[6].

Keratitis

Keratitis is basically the inflammation of the cornea caused by infection in contact lens or any injury caused to the eye. It is also referred by the name "corneal inflammation". It left untreated, it may lead to blindness and is one of the most common causes of blindness all over the world[7]. Virus, bacteria, fungi, and parasite are the most common causative microorganism in the pathogenesis of keratitis[8]. Staphylococcus aureus and Pseudomonas Aeruginosa are the most common causative organism of keratitis. Blurred vision, redness, itching, watery discharge are the most common symptoms of keratitis.

Fluoroquinolone antibiotics such as levofloxacin, gatifloxacin, moxifloxacin is commonly used antibacterial therapy for the management of keratitis[9]

It is commonly advised for patients suffering from keratitis not to use contact lens as infection in contact lens can further worsen the ocular condition.

Eye stye

There are oil producing glands in the eyelids, mainly functioning for lubricating the eye. When any microbe such as bacteria cause infection in this region, the oil producing gland gets obstructed and hence, appears as small bump in either upper or lower part of the eyelids. It is also referred to as hordeolum, Jawad and Taghreed[10]. It can be caused due to unhygienic environment and lack of personal hygiene.

It can cause great discomfort to the eye and cause gritty feeling due to the protruded bump. Redness, swelling and pain are the other significant symptoms of eye stye. There is no specific treatment regimen for eye stye although warm compresses and several ointments are recommended for prompt relief from pain[11].

Corneal ulcers

It is an ocular disease condition in which there is inflammation in the topmost layer of eye[12]. It is one of the leading causes of blindness in the developing countries and is potentially threatening for eye sights[13]. Virus, bacteria, fungi are the major microorganisms responsible for the development of corneal ulcers and sometimes it can be due to allergic reasons or endogenous factors. Use of corticosteroids is also another major reason for the development of corneal ulcers because corticosteroids allow fungi to grow in the corneal region[14]

Blepharitis

Blepharitis is the acute inflammation of the margin of the eyelids and is commonly associated with other ocular conditions such as conjunctivitis, keratitis, and rosacea[15]. It can affect people of any age group and is characterized by burning sensation, irritation, itching, blurred vision,

watering of eyes, and light sensitivity[16]. Eyelid hygiene is a major issue which contributes to blepharitis so hygiene of the eyelid area should be maintained. Cortisone containing ointments and creams can be used for short period of time for managing blepharitis[17].

Uveitis

Uveitis is the inflammation of the uveal tract of the eye which is basically the middle layer of the eye[18]. On the basis of location, uveitis can be classified as anterior and posterior. Anterior uveitis includes iris or ciliary body of the eye while posterior uveitis includes retina and choroid. Various factor can contribute to uveitis include age, sex, genetic factors, and social habits. On the basis of histopathology, uveitis can be granulomatous or non-granulomatous.

Symptoms of uveitis include floaters, pain in the eye, sensitivity to light and ultimately lead to vision loss[19]. Ophthalmoscopy and tonometry can be used for the diagnostic examination of uveitis. Anti-inflammatory treatment regimens and steroid injections are used for the management of uveitis[20].

Dacryocystitis

It is an inflammatory obstructive condition of the lacrimal sac. Due to the obstruction of lacrimal sac, tear fluid gets accumulated and cause inflammation. Pus formation, redness, swelling, pain are the most common clinical symptoms of dacryocystitis[21]. Antibiotics such as ciprofloxacin, clindamycin, amoxicillin, and trimethoprim are used for the management and treatment of dacryocystitis and are commonly administered through oral or intravenous route[22]

Endophthalmitis

It is the bacterial or fungal infection of the inner part of the eye including vitreous and aqueous humor. Exogenous or endogenous factors can be responsible for the occurrence of endophthalmitis[23]. Trauma or surgery can cause endophthalmitis. Endophthalmitis is major seen after cataract surgery. Vitreous humor is more susceptible to attain endophthalmitis rather than aqueous humor because aqueous humor has high turnover rate while vitreous humor does not regenerate that easily[24].

Herpes Zoster ophthalmicus

Herpes zoster ophthalmicus is an ocular infection caused by the microorganism which causes chickenpox in humans i.e, varicella. It mainly affects the trigeminal nerve surrounding area and is one of the most common herpes zoster infections[25]. The elderly patients and the patients with poor immune system are the main suspects of getting Herpes zoster ophthalmicus. It is mainly characterized by ocular inflammation, pain in the surrounding area of trigeminal nerve and ultimately loss of vision. Various antiviral drugs such as acyclovir, famciclovir and others are the first line treatment of Herpes zoster ophthalmicus[26]. Vaccination can also be an important attribute in preventing Herpes zoster ophthalmicus[27]

Optic neuritis

It is one of the most common ophthalmic neuropathies in young adults characterized by demyelination of the optic nerve, ultimately causing inflammation of the nerve[28]. MRI, visual examination, CSF

exams can be done in order to assess or diagnose optic neuritis[29]. It is one of the most common clinical presentations of at least 20% of multiple sclerosis (MS) cases[30] Corticosteroids are commonly used treatment regimen for restoring vision but can be harmful in long term use[31].

2. ANATOMY AND PHYSIOLOGY OF HUMAN EYE

Human eye is basically ball like spherical structure with 23 mm diameter. The anterior, posterior, and tear chambers make up the three primary chambers of the human eye. The retina, choroid, sclera, and vitreous humor make up the posterior chamber while anterior segment of eye comprises of cornea, ciliary body, iris, and aqueous humour[32]**Anterior chamber**

Cornea

It is located in the anterior section of the eye and is the outermost portion, measuring 0.5mm in thickness. It is the generally perceived as a clear visible bulging of the eye. The cornea is made up of five layers: the stroma, endothelium, Bowman's membrane, corneal epithelium, and Descemet's membrane. The cornea does not have blood vessels; instead, it receives its vital nutrients from the capillaries that finish around its perimeter[33]. The cornea's main function is to bend and focus the incoming light entering into the eye which ultimately focuses on the retina[34]

Ciliary body

The nearly triangular ciliary body is made up of ciliary muscles and processes. It has a double coating which is commonly referred to as ciliary epithelium, this ciliary epithelium is responsible for the formation of aqueous humor[35]. The ciliary muscles have important role in adjusting the size of the lens, contraction and relaxation helps in maintaining curvature of the lens.

Iris

Pigmented epithelial cells forms iris part of the eye. The contraction and dilation of pupil is commonly known as miosis and mydriasis respectively. Iris is basically located behind the cornea but in front of the lens[36]. It controls pupil size, allowing for proper adjustment to the amount of light entering the eye. It may be blue, brown, grey, green or hazel in colour.

Aqueous humour

Aqueous humour, basically is jelly-like fluid filled in the outer part of the eye. It is slightly alkaline in nature because it contains trace of sodium and chloride ions. It is present between cornea and lens and it is nutritive and protective in nature. Ciliary processes of the ciliary body mainly produce it continuously. Schemms' canal is mainly responsible for collecting aqueous humour from the anterior chamber and with the help of veins deliver it into the bloodstream[37].

Posterior chamber

Retina

It is located at the backside of the human eye and mainly functions to prepare the image of the object which is formed by light passing through all other parts of the eye before reaching to it. It is light sensitive in nature as it contains photosensitive cells.

Choroid

It generally lies in the space between the sclera and retina. Its main structure consists of many layers such as Bruch's membrane, vessel layers and choriocapillaris[38]. It is highly vascularised i.e., consists of large number of blood vessels, and is brown in colour.

Vitreous humour

It is majorly filled in between retina and lens. It is composed of collagen fibrils and hyaluronic acids. It comprises of approximately 80% part of the human eye and is jelly-like substance or fluid in nature. It is enclosed with delicate membrane known as hyaloid membrane.

Sclera

The white component of the eye is termed sclera and consist of collagen and elastic fibres. It forms the outermost layer of the eye and is globular in shape. It is thinner at the front side while thicker at the back side[39]. Its primary role is to safeguard the eye's other interior organs. It is around maximum 1 mm thick.

3. BARRIERS IN OCULAR DRUG DELIVERY

There are various barriers which hinders the effective delivery of the drug to the ocular surface and these barriers can be categorised as static, dynamic, and metabolic barriers.

The blood aqueous barrier, blood retinal barrier, corneal barrier and retinal pigmented epithelium (RPE) are examples of static barriers in ocular medication delivery. There are multiple layers in the cornea, with the epithelium being the narrowest layer, which do not allow the passage of hydrophilic drugs across it as epithelium is highly lipophilic in nature. RPE serve as barrier to prevent medication from reaching the retina[40]

Another significant barrier to the medication molecules' distribution to the ocular surface is the blood-aqueous barrier as it is composed of tight junction cells which hinders the delivery of hydrophilic molecules across it and also efflux pumps present there continuously pumps out substances from aqueous humour making it more difficult to retain the drug in that region. Similarly, blood retinal barrier also doesn't allow the passage of large molecules across it.

One type of dynamic barrier is the tear film barrier, which quickly washes the medication off the ocular surface and shorten the amount of time the drug is in contact with the surface. Blinking, lacrimal drainage, aqueous humour flow, and choroidal blood flow are also responsible for the rapid wash out of the drug from ocular surface[41]

4. UNDERSTANDING THE COMPLEXITIES OF OCULAR DRUG ABSORPTION MECHANISMS

The topical route of drug administration with the help of eye drops is one of the most common and preferred routes for drug delivery to the cul-de-sac part of the eye. Diffusion, erosion, and dissolution are the three main mechanisms responsible for the availability of the drug in the tear film. Absorption of drug in the ocular surface can be majorly categorized into corneal and noncorneal[42]. For any drug to pass through cornea, the drug should have high aqueous and lipid solubility due to complex

anatomical arrangement of the cornea. Stroma, epithelium, and endothelium are the major barriers encountered in the cornea. Noncorneal route of drug absorption involve movement of drug across sclera and conjunctiva and then ultimately to the tissues and hence not very effective and is also suitable only for drugs having low corneal permeability whereas corneal route of drug absorption involves movement or passage of drugs from cornea to intraocular tissues via aqueous humour.

5. OCULAR DRUG DELIVERY SYSTEM (ODDS)

Human eye has peculiar complex anatomical characteristics which makes it difficult to deliver the therapeutic agent directly to the targeted site in the ocular surface. Various ocular barriers as discussed above hinders the delivery of the drug to desired site and hence drug produces therapeutic effect in inadequate form[43]. Various conventional ocular dosage forms such as drops, ointments, suspensions are common ocular drug delivery regimens as they offer patient compliance due to ease of administration[44]. However, these dosage forms are unable to produce adequate therapeutic effect due to various factors attributed to the washout of the drug from the ocular surface[45].

To overcome this issue of drug washing out from the ocular surface, several strategies such as sustained release with the help of polymers so that prolonged action can be provided. Viscosity and particle size of the formulations are optimized in such a way that drug can be released over extended period of time from the formulation whereas some strategies have been developed to bypass the external barriers of the eye and deliver the therapeutic regimen directly to the anterior or posterior segment of the eye.

To develop a successful and efficacious ocular drug delivery system, it is imperative to have a thorough understanding of the complex anatomical and physiological characteristics of the eye, the physicochemical properties of the drug molecule being used, and the nature of disease for which the therapeutic regimen has been developed[46]. Designing and optimizing the factors accordingly can lead to development of a therapeutic regimen with enhanced therapeutic effectiveness. The other main goal for formulation scientists is to develop and tailor such a therapeutic regimen that can hold or retain the drug at desired site of action for required time, lessen side effects associated with systemic absorption of the drug and also to formulate such regimen which can enhance patient compliance, or do not require any special instructor to administer[47].

6. MODES OF OCULAR DRUG ADMINISTRATION

There can be many routes through which drug can be delivered to the eye but the most important factor in selecting particular route for ocular drug delivery is the targeted site/ tissue of the eye[49]. On the basis of various target tissues, routes of ocular drug delivery can be topical, intracameral, intravitreal, subconjunctival, subretinal, retrobulbar, and systemic route of administration[50].

Topical route

It is one of the most common routes of ocular drug administration, and is usually administered through eye drops. Approximately 95% of the marketed products for ocular drug delivery are administered through this route only as it is non-invasive and also fulfils patient compliance. But the major drawback/ limitation of this route is very short contact time as majority of the fraction of drug gets drained from the eye along with tear fluid. Thus, novel formulations such as in-situ gels, implants have been discovered to prolong the contact time of drug with ocular surface.

Intravitreal route

In this route of ocular drug administration, the drug is directly injected into the vitreous humour part of the eye and thus more efficacious as drug gets direct access to the retina and vitreous humour[51]. But the major barrier in this route of drug administration to deliver the drug to the choroid part is retinal pigmented epithelium (RPE) which restricts the movement of large molecules across it and allows only small molecules to diffuse across it rapidly. Local anaesthetics are commonly employed with this route as it is invasive in nature.

Subconjunctival route

This route of ocular drug administration allows the drug to bypass the epithelium, the main barrier to deliver the drug in ocular region, and hence drug is directly injected under the conjunctiva. Where high drug concentrations are required in ocular surface, this route of ocular drug delivery can be used. The injection given under the eyeball is known as epibulbar and if the injection is given underneath the conjunctival lining, then it is known as sub palpebral.

Intracameral route

It is used basically to deliver the drug to the anterior segment of the eye and overcomes several barriers coming in the way of ocular drug delivery. Various drugs have been administered through this route of ocular drug delivery and have been found to treat the disease efficaciously as the drug concentration in the targeted tissue was found to be increased[52]

Retrobulbar route

It is the route of ocular drug administration in which the drug is directly delivered to the retrobulbar space with the help of injection. In the management of several fungal infections, retrobulbar injection has been found to be more advantageous than intravenous administration.

Systemic administration

It refers to the administration of the drug directly in the bloodstream with the help of intravenous route. But the major drawback of this route of drug administration is that it requires extreme specific dose and requires highly specialized person as once the drug enters the bloodstream, it becomes very difficult to control the therapeutic action if dose is large.

7. NOVEL APPROACHES FOR TARGETED OCULAR DRUG DELIVERY

Various advancements have been done in ODDS to facilitate drug absorption in the eye, and to overcome barriers which hinders the delivery of the therapeutic regimen to the ocular region and to provide sustained release action[53]. Various recently developed ocular drug delivery systems include:

Nanoparticles are novel drug delivery systems composed of biodegradable polymers such as PLGA which helps to deliver and release the drug in a controlled manner[54]

Liposomes are another recent advancement in which both hydrophilic and lipophilic drugs can be encapsulated in phospholipid vesicles so that drug can be easily transported to the lipophilic surface of the eye[55]

Dendrimers are branched structures which traps the drug in those structures and enhance the bioavailability of the drug molecule.

Microneedles are the novel dosage forms which forms microchannels in the ocular surface to enhance the penetration of the drug. Also, dissolving microneedles have the advantage of solid microneedles as the former dissolves after releasing the drug, hence no ocular toxicity can be developed[56]

Hydrogel are systems composed of hydrophilic polymers having the capacity to hold large amount of water and deliver or release the drug in a sustained manner. Hydrogel systems can be of various types such as thermos-responsive and pH-responsive hydrogels.

Contact lenses are such dosage form which are embedded or impregnated with drugs and having the ability to release the drug molecules over extended period of time. Contact lenses can be coated with nanoparticles also so that better control on the release of the drug can be achieved[57].

Implants are another wonderful innovation in the field of ODDS, these are placed in the targeted tissue with the help of minor surgery and are able to release drug for months. Implants can be composed of biodegradable or non-biodegradable polymers, there is no need to remove the implants which are made of biodegradable polymers as degrade within the eye ocular surface while non-biodegradable implants need to be surgically removed.

Gene and RNA based therapies are also efficacious as they utilize viral vectors and mRNAs and can be very helpful in the treatment of genetic ocular diseases[58].

Another major innovation in the field of ODDS to overcome all the barriers and limitations is in-situ gelling systems/ gel forming solution which undergo rapid phase transition from sol to gel upon stimuli activation such as change in temperature, pH, and io-activation[59]

These novel ocular drug delivery system therapeutic regimens are transforming the landscape of ocular therapies and are more convenient and efficacious than regular conventional dosage forms[60].

8. CONCLUSION

The advancement of ocular drug delivery to manage ocular infections with the help of gel forming solutions is highly promising. These are highly efficacious as they provide prolonged drug release, high drug retention

and also improved patient compliance due to less frequency of administration.

Also, with the advancement in polymer science, gel forming solutions are found to be compatible with ocular tissues and are able to deliver various therapeutic antimicrobial agents to the targeted tissues. However, despite of all the advantages offered by these novel dosage forms, the main challenge lies in the maintenance of sterility and scaling up for commercial production. Researchers are continuously employing various gel forming polymers to check their efficacy in sol to gel transition however, in-vivo studies are also required to confirm the safety, efficacy and patient acceptability of these formulations in general population. In conclusion, ocular gel forming solutions are highly promising part of ocular drug delivery system.

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