REVIEW ARTICLE

INTERNATIONAL JOURNAL OF RECENT RESEARCH IN PHARMACY

IJRRP

OCULAR DRUG DELIVERY SYSTEM: STRATEGIES TO IMPROVE BIOAVAILABILITY OF THE EYE

Sonam Baghel[*1], Devender Singh[1], Sakshi Tiwari[1], Deepak Yadav[1], Prabhakar[1] and Shishu Pal[1]

[1]Institute of Pharmacy, Bundelkhand University, Jhansi-284128 (Uttar Pradesh), India

Received- 25/August/2020 **Revised-** 05/September/2020 **Accepted-** 19/September/2020 **Published-** 30/September/2020

ABSTRACT

Topical eye therapy administration is suitable because of the smaller doses that are needed compared to systemic use, its rapid onset of action and the freedom from systemic toxicity. Because of the blood ocular barrier, the route of choice for treating ophthalmic diseases is by the topical method. Ideal delivery of ophthalmic drugs must be able to withstand the release of the drug and stay close to the front of the eye for extended period of time. The solutions, liquids and ointments which are fairly inefficient as therapeutic systems are the most widely used traditional preparations of ophthalmic dosing types. The efforts lead to the development of novel modes of dosage delivery such as formulations of nanoparticles, liposomes, and niosomes. This analysis based on the controlled and sustained delivery of drugs has become the norm in modern pharmaceutical design and many alternative drug delivery routes into the ocular tissues.

KEYWORDS: Ophthalmic preparation, Ocular Drug Delivery System, Anatomy and physiology of eye

Corresponding Author

Sonam Baghel,
Research Scholar, Department of Pharmaceutics, Institute of Pharmacy,
Bundelkhand University, Jhansi-284128 (Uttar Pradesh), India

E-mail: sonam.sona131996@gmail.com

Quick Response Code

INTRODUCTION

The distribution of ophthalmic drugs is the most fascinating and demanding delivery mechanism the pharmaceutical scientist faces [1]. The eye structure, physiology, and biochemistry make this organ particularly impermeable to foreign substances.

A big problem for the formulator is circumventing the eye's defensive defenses without causing irreversible tissue damage. Such barriers have an effect on product bioavailability. The key problem with rapid and complete removal of modern eye drops from the eye is the ocular drug delivery mechanism. This problem leads to substantial drug loss. Only a few drogues penetrate the corneal layer and enter the inner eye tissue. The principal area of drug failure includes lachrymal drainage and tear-dilution of drugs [2]. Optimizing the ocular drug delivery systems includes the following characteristics.

- Great penetration to the cornea.
- Prolonged contact with corneal tissue during the medication.
- Setup and removal simplification for patient.
- A non-irritating and unpleasant type (the viscous solution does not irritate lachrymation and reflex flashes).
- Modified rheological properties and viscolyzer concentration [3].

The main focus from the last two decades is on the advancement of a stable and controlled release drug delivery system. The goal of such a system based on localization at the site of action is to avoid the dose frequency and to boost the drug efficacy [4]. The goal of pharmacotherapeutics at the intended action site is to achieve an appropriate concentration of drugs for a desired

period of time. To reduce the risk of eye injury due to elevated blood concentrations of a medication not intended for eye and local treatment as opposed to systemic therapy, eye as a portal for drug delivery is generally used [5]. The typical methods of eye dosing are eye drops, eye fluids, eye gels, eye pain treatments, eye treatments, eye ointments, eye injections, gel sol systems [6]. Eighty per cent of overall ophthalmic treatments are most commonly used eye drops, skin ointments, and gels.

The eye drop dosage type is simple to instil but has drawbacks such as repeated administration requirements, rapid precorneal removal, gluing of the eye lids, erratic doses, medication loss due to drainage, blurry vision, no true lasting effect, eye discomfort and poor patient compliance [7, 8, 9]. It is usually reasonable that the intraocular bioavailability of topically applied drugs is extremely low, ranging from 5 to 10 percent of the total administered [10, 11, 12].

Advantages of Ocular Drug Delivery Systems[13]

- ✓ Precise dosing increased. Can surmount the side effects of modern pulsed dosing.
- ✓ To ensure a continuous and regulated distribution of medicines.
- ✓ To improve the drug's eye bioavailability by increasing the duration of contact with the cornea. This can be accomplished by strong adhesion to the surface of the cornea.
- ✓ To include targeting of other ocular tissues inside the eye globe to avoid failure.
- ✓ To overcome safety barriers such as drainage, lacrimation, and conjunctival absorption.
- ✓ To provide convenience, increase patient compliance and enhance the drug's therapeutic efficiency.
- ✓ To offer better distribution system accommodation.
- ✓ They themselves can be easily administered by the patient.
- ✓ They have the rapid absorption and less side effects visually and systemically.
- ✓ Ocular drug delivery system is more compatible with patients.

Disadvantages of Ocular Drug Delivery System[14]

- ❖ The drug solution stays in the surface of the eye for very short time.
- ❖ The bioavailability shows bad.
- ❖ The dissolved drug shows instability.
- ❖ The use of condoms is required.

Limitations of Ocular Drug Delivery [14]

- ➢ Cannot avoid the medication process during an emergency.
- ➢ Vision deficiency.
- ➢ Difficulty putting and removing.
- ➢ Occasional loss while sleeping or rubbing eyes.

The Anatomy of the Eye

This universe is very beautiful because we can see it, we can feel it. The eye is a unique organ, both anatomically (**Figure 1**), and physiologically, containing several widely varied structures with independent physiological functions [15, 16].

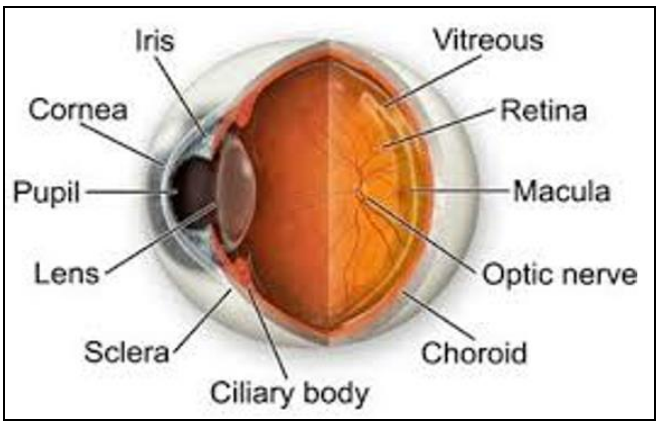

Figure 1: Structure of Eye

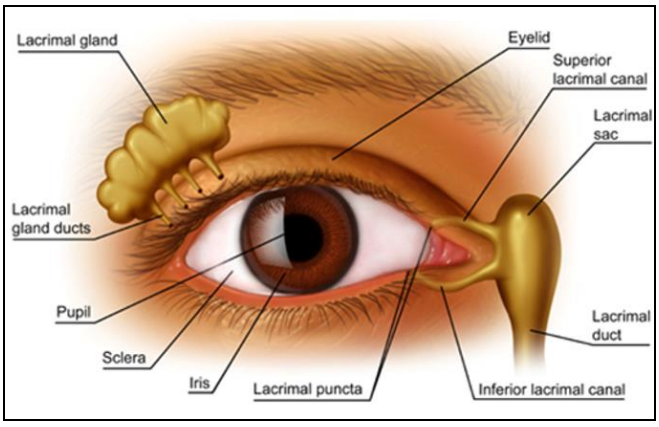

Figure 2: Accessory Structures of Eye

Accessory Structures

The eye's accessory (adnexal) structures include the eyelids, conjunctiva, caruncle and lachrymal (tear) glands, eye accessory structures as shown in **Figure 2**.

Table 1: List of Various Parts of Eyes and its Importance

S. No.	Parts	Importance
1	Sclera	The sclera is the thick, white connective tissue, which covers much of the eyeball outside. The sclera is known as the eye's white part, which serves as the protective shield. Across the back of the eye, the optic nerve and blood vessels cross the sclera. Muscles which control the eye's movement bind to the sclera [17].
2	Cornea	The cornea, on the front of the head, is the transparent, dome-shaped covering that lets light. The cornea stretches over the eye and the iris. It contains no blood vessels [18].
3	Ciliary body	The ciliary body lies just behind the iris and extends out from the choroid. It is the muscular tissue ring which helps the focus of the eye. This shifts the lens' shape, so it can focus on objects near or far away. The ciliary body includes cells that produce aqueous humor, which is the transparent fluid between the cornea and the lens at the front of the eye [19].
4	Iris	The iris is a thin contractile circular veil, situated in front of the lens but behind the cornea. The iris is a variable-sized diaphragm whose function is to adjust the pupil's size to regulate the amount of light admitted into the eye. This is the colored portion of the eye (shades, including blue, green, brown, hazel, or black, will differ individually) [20].
5	Pupil	Pupil tends usually to be the dark "middle" of the eye but can be defined more accurately as the circular aperture in the center of the iris through which light passes into the eye. Pupillary reflex (also known as the "light reflex") regulates the size of the pupil (and thus the amount of light that is admitted into the eye) [20].
6	Choroid	The choroid is a thin layer of tissue containing many tiny blood vessels which supply the retina with oxygen and nutrients. The choroid contains many cells producing pigment named melanocytes. Such cells help to absorb any excess light and reduce intraocular reflections [21].
7	Optic nerve	The optic nerve (a bundle of more than 1 million nerve fibers) transmits nerve impulses from the eye to the brain. Such nerve impulses provide information about an image for the brain to interpret. The optic nerve's front surface, visible on the retina, is called optic disc.
8	Lens	The lens is a transparent structure which lies directly behind the cornea and iris in the inner part of the eye. The shape of the lens varies to make the eye focus on objects. The lens concentrates light rays on the retina [22].
9	Vitreous Humour	The vitreous humor (also known as the vitreous body) is located in the wide area of the human body which occupies around 80 per cent of each eye. The vitreous humour is a thin-jelly-like material that is completely translucent and fills the cavity behind the eye lens. It is an albuminous substance that is wrapped in a delicate translucent membrane called the hyaloid cone.
10	Macula	The retina center is called the macula. The macula contains a high photoreceptor cell concentration which converts light into nerve signals. Thanks to the high photoreceptor concentration, fine information such as newsprint with the macula can be seen with us. The fovea, the position of our most clear vision, is at the very middle of the macula.
11	Retina	The retina sits at the back of the human eye. The retina can be represented as the "screen" on which the light that passed into the eye through the cornea, aqueous humor, pupil, lens, and finally the vitreous humor before reaching the retina is created. The function of the retina is not only to be the screen on which an image can be created, but also to capture and relay the information stored in that image to the brain in an acceptable way for the body to interpret it. Therefore, the retinal "screen" is a light-sensitive structure which lines the eye's interior. It contains photosensitive cells (called rods and cones) and their associated nerve fibers which convert the light they detect into nerve impulses which are then transmitted along the optic nerve to the brain.

Table 2: List of Various Accessory Parts of Eyes and its Importance

S. No.	Parts	Importance
1	Eyelids	The eyelids (palpebrae) are skin folds that cover and guard the eye. The eyelids contain glands that create an oily secretion that covers the layer of tears and prevents tears from evaporating and the eyelids from sticking together [23].
2	Conjunctiva	The conjunctive applies to eye covering. It helps to lubricate the eye by secreting mucous and tears, and again uses microbes as a defensive barrier. It contains several goblet cells that secrete an eye-bathing portion of the tears.
3	Eyelashes	Eyelashes are short curly, stiff hairs which can occur in double or triple rows. They work to protect the eye against debris. Lashes can also have lengths and diameters different from one another.
4	Lacrimal gland	The lacrimal glands are the storage centers for the tears. Tears help to keep the epithelium of the conjunctive and corneal moist and to wash away foreign material from the eye. The tear film covering the corneal surface is a mixture of proteins, enzymes, lipids, metabolites, electrolytes and (secreted during therapy) medicines.
5	Extraocular muscles	Extraocular muscles (muscles outside the body) make it possible for the body to move in its orbit. Six of these muscles of the eyeball fasten to each eye. The movements of these two eye muscles are synchronized so that the eyes can move in unison, a phenomenon known as the conjugate gaze [24].

Routes of Ocular Drug Delivery

There are several potential drug delivery routes inside the ocular tissues. The choice of route of administration mainly depends on the target tissue.

Topical

Normally, eye drops achieve topical ocular drug administration, but they only have brief contact duration on the surface of the skin. Contact can be extended by formulation design (e.g. gels, gelifying formulas, ointments, and inserts) and hence the duration of drug action.

Intravitreal

Direct administration of the medication into the vitreous provides a distinct benefit of better access to the vitreous and retina. It should be noted; however, transmission from the vitreous to the choroid is more complicated because of the RPE (Retinal Pigment Epithelium) barrier impediment. Small molecules can spread rapidly in the glass, but the mobility of large molecules is limited, especially positively charged [25].

Intra Cameral

The path within a chamber for drug administration, such as the eye's anterior or posterior chamber. Example: injection of an esthetic into the eye's anterior chamber, normally during surgery.

Peril Ocular

This is the path by which drug administration across the eye is called ocular risk. Example: perilous ocular steroid injection includes placing steroid around the eye to treat intraocular inflammation or eye swelling.

Suprachoroidal

Drug administration at the supra choroid region of the eye. The space between the sclera and the choroid is suprachoroidal.

Sub Conjunctiva

The way the drug is delivered to the mucus membrane, which covers the exposed portion of the eyeball and the inner surface of the eyelids.

Systemic

The blood aqueous barrier and the blood retinal barrier are the primary obstacles for the anterior and subsequent eye drug delivery segments respectively [26].

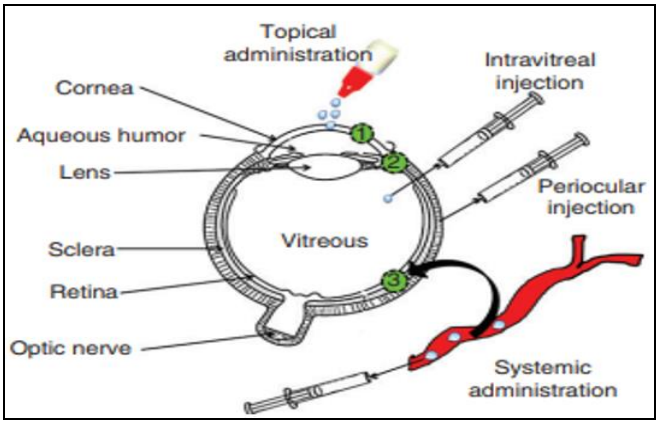

Figure 3: Routes of Administration Ocular Drug Delivery [27]

Barriers to Drug Permeation

The human eye has a spherical shape with a diameter of 23 mm. The eyeball's structural components are divided into three layers: the outermost coat consists of a clear, transparent cornea and a white, opaque sclera; the middle layer consists of the anterior iris, the posterior choroid and the ciliary body; and the inner layer consists of the retina, which is an extension of the central nervous system.

1) Ocular Surface Barriers

The superficial layers of the cornea and conjunctival form the eyepiece that is in contact with the tear film. The eyepiece surface is designed to create a protective barrier against undesired molecules. The surface of the cornea is only 5 % of the total eye surface and the remaining 95% are occupied by the conjunctive [28]. The cornea consists of five layers (a) epithelium, (b) layer of Bowman, (c) stroma, (d) membrane of Descemet, (e) endothelium, but only the outermost layers of the corneal squamous epithelial cells form a barrier to intercellular penetration of drugs [29].

2) Ocular Wall Barriers

The eye globe skeleton consists of a rigid collagenous scleral membrane, which is internally filled by the uveal tract. Save for a small posterior opening filled by the optic nerve ear, the sclera covers the posterior 80 per cent of the eye globe, while the remainder of the globe is covered by the cornea anteriorly. The scleral stroma consists of bundles of collagen, fibroblasts and a small quantity of ground material. This tissue is basically a vascular but the vascular episclera is superficially lined. The sclera is penetrated by a large number of channels to allow the vessels and nerves to pass to the choroid side.

The scleral thickness in humans varies from 0.3 to 1.0 mm with the posterior polar being the thickest [30]. The choroid is a highly vascularized tissue, one of the highest levels of blood flow among body tissues. This layer thickness averages 0.25 mm and consists of a layer of fenestrated chorio-capillaris, medium and large outer vessels (both non-fenestrated) [31].

3) Retinal Barriers

The retina consists of 10 layers: (a) the Retinal Pigment Epithelium, (b) the outer photoreceptor cells, (c) the outer limiter membrane, (d) the outer plexiform layer, (e) the inner plexiform layer, (g) the inner plexiform layer, (h) the ganglion cell layer, I the nerve fiber layer, (j) the inner limiter membrane [32].

4) Physical Approaches to Improve Ocular Bioavailability: Formulation Approaches (Industrial Perspective)

Conventional Ophthalmic Dosage Forms

Solutions are commonly used drug formulations for the topical medicinal delivery to the body. Factors to be considered in formulating ophthalmic solutions include solubility, eye toxicity, pKa, pH effect, tonicity, buffer ability, viscosity, compatibility with other ingredients in the formulation, preservatives to be used, eye comfort and ease of production [33].

Eye Ointments

Ointments are typically formulated using semi-solid and solid hydrocarbon (paraffin) mixtures that have a melting or softening point close to body temperature and are eye-free. Ointments may be simple bases in which the ointment forms a continuous phase or hybrid bases in which a two-phase structure (e.g. an emulsion) is used. The medicinal agent is applied to the base either as a solution or as a finely micronised powder. Ointments break up into small droplets after instillation in the eye and linger in the cul-de-sac as a drug depot for prolonged periods. Therefore, it is helpful in enhancing the bioavailability of medicines and preserving ointments for medication release. Although safe and well-tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation [34].

Prodrug

The prodrug concept is to increase the permeability of corneal drugs by adjusting the drug's hydrophilicity (or lipophilicity). The prodrug is either chemically or enzymatically metabolized into the active parent compound within the cornea, or after corneal penetration. So, not only would the ideal prodrug have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility. Example: antiviral medications ganciclovir and acyclovir are the suitable prodrug [35].

Viscosity Enhancers

Normally, polymers are added to ophthalmic drug solutions that increase the viscosity on the premise and lead to a slower removal from the worried region, resulting in improved precorneal residence time and hence greater transcorneal penetration of the drug into the anterior chamber. This has limited effects in humans in terms of enhancing the bioavailability. The polymers used are methylcellulose, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), hydroxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), and hydroxypropyl cellulose. Natural polymers such as HA, veegum, alginates, xanthan gum, gelatin, acacia, and tragacanth can also be used as viscosity enhancers. However, these suffer the drawback of harboring bacteria and fungi [36].

Penetration Enhancers

By enhancing the permeability of the corneal epithelial membrane, it is possible to improve the transport characteristics across the cornea, thereby improving the bioavailability of ophthalmic drugs, one of the methods used to increase the permeability characteristics of the cornea with suitable substances called penetration enhancers or absorption promoters.

Many drawbacks of it are like ocular pain and toxicity. The process of transporting from the cornea to the receptor site is a rate-limiting step, and permeation enhancers increase corneal absorption by modifying the integrity of the corneal epithelium [37].

5) Emulsions

The emulsion-based formulating approach provides the benefit for both enhancing product solubility and bioavailability. There are two types of emulsions that are exploited commercially as active pharmaceutical vehicles: oil in water (o/w) and water in oil (w/o) emulsion systems. Emulsion is popular for ophthalmic drug delivery

and is commonly favoured over w/o system. The reasons include less irritation and better ocular tolerance of o/w emulsion [38].

6) Microemulsions

Microemulsions are water and oil dispersions enabled by a combination of surfactant and co-surfactant in a manner that decreases interfacial stress. Usually these systems are characterized by high thermodynamic stability, minute drop size (about 100 nm) and clear appearance [39]. An analysis of the application of microemulsions in the provision of ocular drugs by Vandamme *et al*., deals scientifically with the variety of developments and challenges happening in the ground. Aqueous phase range, organic phase, and surfactant / co-surfactant systems are important parameters which may affect system intensity. Optimization of these components results in major increases in drug molecule solubility e.g. indomethacin, chloramphenicol [40].

7) Suspensions

Suspensions are another class of topical drop drug carrier system that are not harmful to the ocular. Suspension can be defined as dispersion of finely divided, insoluble API into an aqueous solvent consisting of an appropriate suspending and dispersing agent. To put it another way, the carrier solvent method is a saturated API solution. Particles in suspension remain in the precorneal pocket and thus increase the frequency and length in drug interaction and the duration of action compared to drug solution. Length of drug action for suspension is dependent on particle size. Smaller particles replenish the drug that is absorbed from the precorneal pocket into ocular tissues [41]. Whereas on the other hand the greater particle size tends to preserve particles for longer periods of time and delay removal of substances. Therefore, optimum particle size is supposed to contribute to optimal drug activity. Many types of suspension are sold worldwide to treat infections of the ocular bacteria. TobraDex suspension is one of the commonly accepted commercial items for steroid therapy responding subjects.

Novel Ophthalmic Dosage Forms

1) Liposome

Liposome is a biocompatible and biodegradable lipid vesicle made of natural lipids, with a diameter of around 25-10,000 nm. They have a close interaction with the corneal and conjunctive surfaces, which is ideal for poorly absorbed drugs, low partition coefficient drugs, weak solubility or medium to high molecular weights, thereby increasing the risk of ocular drug absorption [42]. The corneal epithelium is thinly coated with negatively charged mucin which the liposome's positively charged surface can bind to. Formulated and tested ciprofloxacin-coated flexible contact lenses embedded in liposome.

2) Nanomicelles

The nanomicelles are nano-sized carrier structures constructed from monomer amphiphilic components. These can be based on surfactants or polymers and include hydrophobic medications. Wonderful attention has been paid to nanomicellar formulations due to ease of preparation, high drug usage, improved bioavailability of therapeutic molecules [43].

Patrizia Chetoni determines whether tobramycin as an ion-pair incorporated in Solid Lipid Nanoparticles (SLN) mucoadhesive reaches the inner parts of the eye which favor drug activity. Following technical characterization of tobramycin trapped SLN formulation (Tobra-SLN), after topical instillation and intravenous formulation administration, pharmacokinetic work in rabbits was conducted. In addition, the intracellular activity of the Tobra-SLN formula against phagocytised Pseudomonas aeruginosa was assessed [44].

3) Niosomes

These are bilayered, lamellar structures composed primarily of non-ionic surfactants and a rigidizing agent, which are hydrated by various methods to form a vesicle. These are either unilamellar or multilamellar, with an aqueous pocket enclosed. The non-ionic surfactants, being amphiphilic in nature, are considered to possess the ability to assemble themselves. Critical parameters in the preparation of niosomes control the creation of vesicular structures, rather than micelles [45, 46]. The non-ionic surfactants in nature cause no damage to the ocular tissue and their ability to act as penetration enhancers can be exploited as well.

4) Implants

Intraocular implants are primarily designed for provision over a prolonged period of localized managed drug release. Such tools help to prevent multiple intraocular injections and associated complications [47, 48]. Usually for drug

delivery to posterior ocular tissues, implants are placed intravitreally by making incision through minor surgery at pars plana which is located posterior to the lens and anterior to the retina. Although implantation is an invasive procedure, these devices are gaining interest due to their associated advantages such as sustained drug release, local drug release at therapeutic levels to diseased ocular tissues, reduced side effects and the ability to circumvent the blood retina barrier [49]. Several implantable devices were developed for the delivery of ocular drugs, in particular for chronic vitreoretinal diseases treatment.

5) Nanosuspensions

It has emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they have improved not only the rate and degree of ophthalmic drug absorption but also the strength of drug action with substantial extended drug effect period [40]. Techniques such as media milling and high-pressure homogenisation have been used for the industrial preparation of nanosuspensions. The higher drug level in aqueous humor was recorded for the ophthalmic controlled delivery of ibuprofen using Eudragit RS 100 nanosuspensions.

Eye Infections

Eyes can get bacterial, fungal or viral infections. Infections of the eye can occur in areas of the body and can affect either one or both eyes. Conjunctivitis, Corneal ulcers & Endophthalmitis are common eye infections.

A) Conjunctivitis:

Conjunctivitis is swelling (inflammation) or eyelid lining (conjunctive) membrane infection. It is characterized by penetration and exudation by the cells. *Staphylococcus aureus* is the most common cause of the conjunctivitis and blepharo-conjunctivitis of bacteria. Many other organisms like *Haemophilus influenzae*, *Streptococcus pneumoniae* also cause conjunctivitis. Conjunctivitis can be classified as

- Infective – Acute, Subacute & Chronic
- Allergic conjunctivitis.

B) Corneal ulcers/ Keratitis

Corneal inflammation (Keratitis) is characterized by corneal oedema, cell infiltration & ciliary congestion. Since cornea is the most anterior portion of the eyeball, it is exposed to the environment and is thus easily infected. Virulent organisms are the most common causes of bacterial corneal ulcers. Common bacteria associated with corneal ulceration are *Staphylococcus aureus, Pseudomonas pyocyanea*, *E. coli* and *Proteus* etc.

C) Endophthalmitis

It is a serious type of intraocular inflammation (purulent uveitis) that includes eye cavities & inner eyeball coats. Causes include *Streptococci*, *E. coli*, *Pseudomonas*, etc. Accordingly, the armamentarium of antimicrobials being used to prevent and treat such infections includes antivirals, antifungals, and antibacterial. Popular topical antibacterial used in the treatment of infectious ocular diseases include sulphonamides, aminoglycosides, combinations of polymyxin and fluoroquinolones [25].

Management of Ocular Infections

Eye infections, both superficial and deep, such as conjunctivitis, corneal ulcers and endophthalmitis, are caused by a variety of bacteria, viral and fungal pathogenic groups. Accordingly, the armamentarium of antimicrobials being used to prevent and treat such infections contains antivirals, antifungals, and antibacterial. Popular topical antibacterial used in the treatment of infectious ocular diseases include sulphonamides, aminoglycosides, formulations based on polymyxin, and fluoroquinolones. For serious bacterial keratitis, endophthalmitis, blepharo-conjunctivitis, corneal ulcers, chronic post-filtration hypotony etc., these fluoroquinolones are indicated.

Fluoroquinolones are an expanding class of antibacterial broad spectrum that covers a host of Gram negative and anaerobic species responsible for ocular infections. These antibacterial have gained popularity in the field of ophthalmology, since many ocular infections have been shown to be equivalent to combination therapy. Fluoroquinolones are also effective against a variety of Gram-positive organisms including Streptococcal and Staphylococcal species [50].

Fluoroquinolones deliver all the attributes of an ideal antimicrobial agent including broad antimicrobial range, strong tissue penetration and bioavailability, high clearance levels, chemical and biological stability, low toxicity, high binding affinity to melanin, increased patient compliance,

easy dose and dose schedule and fairly low occurrence of drug interactions.

CONCLUSION

Increasing the residence time on the corneal surface of an ophthalmic formulation increases the bioavailability of the drug and thereby decreases the frequency of administration. Ultimately, I concluded that designing the ophthalmic solutions is a revolutionary approach to the ocular drug delivery system as we can effectively target the eye to treat oculary diseases with a wide range of novel approaches. Recently progress has been made in the field of eye drug delivery, with controlled loading and sustained release. As a traditional drug delivery system, successful drug delivery and targeting are thus faced with obstacles to resolve these barriers.

ACKNOWLEDGEMENT

Authors are thankful to Mr. Devender Singh, Department of Pharmaceutics, Institute of Pharmacy, Bundelkhand University, Jhansi for his valuable suggestion in writing this paper.

CONFLICT OF INTEREST

None

REFERENCES

1. Zaki I, Fitzgerald P, Hardy JG and Wilson CG. "Comparison of effect of viscosity on the precorneal residence of solution in rabbit and man". Journal of Pharmacy and Pharmacology (JPP), 1999; 38, pp. 463-466.
2. Lee VH and Robinson JF. "Review: Topical ocular drug delivery; recent developments and future challenges". Journal of Ocular Pharmacology and Therapeutics (JOPT), 2009; 2, pp. 67.
3. Keister JC, Cooper ER, Missel PJ, Lang JC and Hager DF: "Limits on optimizing ocular drug delivery". Journal of Pharmaceutical Science (JPS), 1991; 80, pp.50-53.
4. Sikandar MK, Sharma PK and Visht Sikandar S. "Ocular drug delivery system: an overview". International Journal of Pharmaceutical Sciences and Research (IJPSR), 2011; 2, pp. 1168-75.
5. Saettone MF and Salminen L. "Ocular inserts for topical delivery". Asian Journal of Pharmaceutics (AJP), 2001; 16, pp. 95-106.
6. Schoenwald RD. "Ocular Pharmacokinetics/ Pharmaco-dynamics". Ophthalmic drug delivery systems. Marcel Dekker, New York, 2003; pp. 260-65.
7. Neefe CW. "Contact lens for ocular drug delivery". US Patent. 1974; 3, pp.786–812.
8. Gibaldi M and Perrier D. "Pharmacokinetics: Drugs and the pharmaceutical sciences" Marcel Dekker, New York, Edition 2nd, 1993; 15, pp.1000-08.
9. Robinson JC. "Ocular anatomy and physiology relevant to ocular drug delivery". Ophthalmic Drug Delivery Systems. Marcel Dekker, New York, 2002; pp. 573-79.
10. Chien YW. "Novel drug delivery systems". 2nd edition. Marcel Dekker, New York. Edition 2nd, 2003; pp. 301.
11. Khar RK and Vyas SP. "Targeted and controlled drug delivery novel carrier systems. C.B.S. Publishers and Distributors, New Delhi, Edition 1st, 2002; pp. 111.
12. Mainardes RM, Urban MC, Cinto PO and Chaud MV. "Colloidal carriers for ophthalmic drug delivery". Current Drug Targets (CDT), 2017; 6, pp. 363–371.
13. Reddy KR, Shankar R, Yadav M and Reddy PS. "Preparation and evaluation of aceclofenac ophthalmic *in-situ* gels", Journal of Chemical, Biological and Physical Sciences (JCBPS), 2011; 1(2), pp. 289-298.
14. Katariya DC and Poddar SS. "Current status of ophthalmic *in-situ* forming hydrogel". International Journal of Pharma and Bio Sciences (IJPBS), 2012; 3(3), pp. 372-388.
15. Mitra AK. "Ophthalmic drug delivery systems". Marcel Dekker, New York, 2003; pp. 704.
16. Reddu IK. "Ocular therapeutics and drug delivery": CRC Press, 1995.
17. Kamel A. "*In-vitro* and *in-vivo* evaluation of Pluronic F127 based ocular delivery system for timolol maleate". International Journal of Pharmaceutics (IJP), 2002; 24 (1), pp.47-55.
18. Saini R. "*In-situ* gels a new trend in ophthalmic drug delivery systems". International Journal Recent Advanced Pharmaceutical Research (IJRAPR), 2015; 5 (3), pp. 285-289.
19. Jitendra PK, Sharma A, Banik and Dixit S. "A new trend ocular drug delivery system". International Journal of Pharmaceutical Sciences (IJPS), 2011; 2(3), pp.720-744.
20. Nanjawade BK, Manvi FV and Manjappa AS. "*In-situ*-forming hydrogels for sustained ophthalmic drug delivery". J Cont Rel (JCR), 2007, 122, pp. 119-34.
21. Pandya TP, Modasiya MK and Patel VM, "Ophthalmic *in-situ* gelling system". International Journal of Pharmacy & Life Sciences (IJPLS), 2011; 2(5), pp. 730-738.
22. Jain R and Shastri P. "Study of ocular drug delivery system using drug loaded liposomes". International Journal of Pharmaceutical Science Investigation (IJPSI), 2011; 1(1), pp. 234-244.
23. Vandamme TF, "Microemulsions as ocular drug delivery systems recent development". Sch Acad J Pharm (SAJP), 2015; 4(7), pp.340-346 346
24. https://healthengine.com.au/info/the-eye-and-vision
25. Dhanapal R and Ratna JV. "Ocular drug delivery system – a review". International Journal of Innovative Drug Discovery (IJIDD), 2012; 2(1), pp. 4-15.
26. Liang H, Brignole-Baudouin F, Rabinovich Guilatt L, Mao Z, Riancho L, Faure MO, Warnet JM, Lambert G and Baudouin C. "Reduction of quaternary ammonium induced ocular surface toxicity by emulsions: an *in-vivo* study in rabbits". Mol Vis (MV), 2008; 14, pp. 204-216.
27. Bisht R, Mandal A, Jaiswal JK and Rupenthal ID. "Nanocarrier mediated retinal drug delivery: overcoming ocular barriers to treat posterior eye diseases". WIREs Nanomed Nanobiotechnol (WNN), 2017; pp. e1473. doi: 10.1002/wnan.1473
28. Karesh JW. "Topographic anatomy of the eye". Foundations of Clinical Ophthalmology (FCO), 2003; 1, pp. 1-16.
29. Smolek MK and Klyce SD: Cornea of Clinical Ophthalmology (CCO), 2003; 1, pp.1-10.
30. De la Maza MS and Foster CS. "Sclera". Foundations of Clinical Ophthalmology. Philadelphia: Lippincott Williams & Wilkins, Chapter 1.
31. Buggage RR, Torczynski E and Grossniklaus HE: "Choroid and suprachoroid". Foundations of Clinical Ophthalmology (FCO), 2003; 1, pp.1-10.
32. Park SS, Sigelman J and Gragoudas ES. "The anatomy and cell biology of the retina". Foundations of Clinical Ophthalmology (FCO), 2002; 1, pp. 1-10.

33. Lee VH. "Precorneal, corneal and postcorneal factors". Ophthalmic Drug Delivery Systems. Marcel Dekker, New York, 2012; pp. 59-82.
34. Lee VH. "Evaluation of ocular anti-inflammatory activity of *Butea frondosa*". Journal of Pharmacy and Pharmacology (JPP), 2011; 11, pp. 79-90.
35. Vandamme TF. "Microemulsions as ocular drug delivery systems: recent developments and future challenges". Journal of Pharmacy and Pharmacology (JPP), 2015; 21, pp. 15–34.
36. Sasaki H, Igarashi Y, Nagano T, Yamamura K, Nishida K and Nakamura J. "Improvement of the ocular bioavailability of timolol by sorbic acid". Journal of Pharmacy and Pharmacology (JPP), 2009; 47, pp.17-21.
37. Tirucherai GS, Dias C and Mitra AK. "Effect of hydroxypropyl beta cyclodextrin complexation on aqueous solubility, stability, and corneal permeation of acyl ester prodrugs of ganciclovir". Journal of Ocular Pharmacology and Therapeutics (JOPT), 2012; 18, pp. 535-48
38. Law SL, Huang KJ and Chiang CH. "Acyclovir-containing liposomes for potential ocular delivery. Corneal penetration and absorption". J Control Release (JCR), 2000; 63, pp. 135-140.
39. Vandamme TF. "Microemulsions as ocular drug delivery systems: Recent developments and future challenges". Prog Retin Eye Res (PRER), 2002; 21, pp.15–34.
40. Kataria S, Middha A, Sandhu P, Bilandi A and Kapoor B. "Microsphere: A review". Int J Res Pharm Chem (IJRPC), 2011; 1(4), pp.1184-1198.
41. Rajoria G and Gupta A. *In-situ* gelling system: A novel approach for ocular drug delivery". AJPTR, 2012; 2: pp.24–53.
42. Dwivedi C, Sahu R, Tiwari S, Satapathy T and Roy A. "Role of liposome in novel drug delivery system". Journal of Drug Delivery and Therapeutics (JDDT), 2014; 4(2), pp.116-129. doi:10.22270/jddt.v4i2.768
43. Foziyah Z, Singh M and Iqbal Z. "Ocular drug delivery: Recent updates". International Journal of Drug Regulatory Affairs (IJDRA), 2016; 4(4), pp. 15-22.
44. Susi B and Daniela M. "Solid lipid nanoparticles as promising tool for intraocular tobramycin delivery: Pharmacokinetic studies on rabbits". European Journal of Pharmaceutics and Biopharmaceutics (EJPB), 2016; 109, pp. 214-223.
45. Chauhan MK and Yenamandra J. "Management of glaucoma: effective drug delivery via Niosomes", Journal of Drug Delivery and Therapeutics (JDDT), 2016; 6(6), pp. 48-53 DOI: http://dx.doi.org/10.22270/jddt.v6i6.1313
46. Tham Y C, Li X, Wong TY, Quigley AH, Aung T and Cheng CY. "Global prevalence of glaucoma and projections of glaucoma burden through 2040 A systematic review and meta-analysis". Ophthalmology (O), 2014; 121(11), pp.2081-2090
47. Bourges JL, Bloquel C, Thomas A, Froussart F, Bochot A, Azan F, Gurny R, BenEzra D and Behar-Cohen F. "Intraocular implants for extended drug delivery: therapeutic applications". Adv Drug Deliv Rev (ADDR), 2006; 58, pp.1182–1202. 10.1016/j.addr.2006.07.026 [PubMed: 17107737]
48. Del Amo EM and Urtti A. "Current and future ophthalmic drug delivery systems. A shift to the posterior segment". Drug Discov Today (DDT), 2008; 13, pp. 135-143.10.1016/j.drudis.2007.11.002 [PubMed: 18275911]
49. Lee SS, Hughes P, Ross AD and Robinson MR. "Biodegradable implants for sustained drug release in the eye". Pharm Res (PR), 2010; 27, pp.2043–2053.10.1007/s11095-010-0159-x [PubMed: 20535532]
50. Gupta P, Vermani K and Garg S. "Hydrogels: from controlled release to Ph responsive drug delivery". Drug Discov Today (DDT), 2002; 7, pp. 569-79.

How to cite this article:

Baghel S, Singh D, Tiwari S, Yadav D, Prabhakar and Pal S. "Ocular drug delivery system: strategies to improve bioavailability of the eye". International Journal of Recent Research in Pharmacy (IJRRP), 2020; 1(1A), pp. 31-39.