

Revolutionizing Eye Care: A Review of Modern Ocular Drug Delivery Strategies

Prof. (Dr.) Abhishek Kumar Sen¹ and Mr. Kashaf Pathan²

Principal & Professor, Pratibhatai Pawar College of Pharmacy Shirampur, Ahilyanagar, Maharashtra, India¹

Student, Pratibhatai Pawar College of Pharmacy Shirampur, Ahilyanagar, Maharashtra, India²

Abstract: *The major challenge faced by today's pharmacologist and formulation scientist is ocular drug delivery. Topical eye drops are the most convenient and patient-compliant route of drug administration, especially for the treatment of anterior segment diseases. Delivery of drugs to the targeted ocular tissues is restricted by various precorneal, dynamic and static ocular barriers. Also, therapeutic drug levels are not maintained for a longer duration in target tissues. In the past two decades, ocular drug delivery research has rapidly advanced towards developing a novel, safe and patient-compliant formulation and drug delivery devices/techniques, which may surpass these barriers and maintain drug levels in tissues. Anterior segment drug delivery advances are witnessed by the modulation of conventional topical solutions with permeation and viscosity enhancers. Also, it includes development of conventional topical formulations such as suspensions, emulsions and ointments.*

Keywords: Cornea; Emulsions; Implants; Liposome; Nanomicelles

I. INTRODUCTION

Human eye is a complex structure, both anatomically and physiologically, that makes it a unique organ consisting of its physiologically independent functions. Its wide range of varied structures also challenges to develop drug delivery systems for it. The major problem in the conventional ocular drug delivery system with eye drops is their fast and extensive elimination from the eye, causing extensive loss of the drug [1,2]. In eye drops, only a small portion of a drug penetrates through the corneal layer and arrives in the internal tissues present in the eye [3,4]. Broad classification of ocular drug delivery results in two types, those concerned with the anterior and posterior segments.

For vision threatening ocular diseases, conventional drug delivery systems, such as eye drops, suspensions and ointments, cannot be used for optimal treatment [5]. About 90% of the ophthalmic formulations in the market are available in the form of eye drops and the sites of action are diseases occurring in the anterior segment of the eye [6]. Topical delivery of drugs through conventional approaches is unable to make it reach the posterior segment of the eye. Formulations like eye drops and ointments, when instilled into the cul-de-sac, are wiped away from eye region quickly because of the flow of tear and lachrymal nasal drainage. Most of the drug is drained away and only a small portion reaches the site of action; so, it needs frequent dosing to achieve a therapeutic effect.

The eye's posterior segment includes the retina, vitreous humour and choroid; the diseases occurring in these regions can be cured by using intravenous and intravitreal drug delivery systems, implants or by administering drug through periocular route and needs high concentration of the drug as well. For ophthalmic drug delivery, the posterior segment of eye is frequently a choice of interest to locate drugs using novel approaches [7].

The rationale behind this review and novelty of this study are to highlight the newer developments in the pharmaceutical ophthalmic formulations, such as formulation of in situ gels, nanoparticles, liposomes, nanosuspension, microemulsion, ocular inserts and so on, and their progress to overcome the problems associated with the existing conventional dosage forms and also to improve the bioavailability as well as the sustained release of the drug at the target location [8].



Anatomy of the Eye

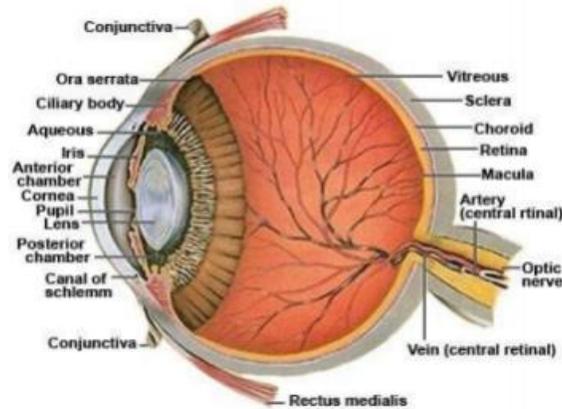


Figure 1. Anatomy of The Eye

The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical in shape and about 1 inch across. It houses many structures that work together to facilitate sight. The human eye is comprised of layers and internal structures, each of which performs distinct functions. The detailed description of each eye part is given below.

1. Sclera

The sclera (white portion of the eye) is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is much thicker towards the back/posterior aspect of the eye than towards the front/anterior of the eye.

2. Conjunctiva

The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids, and covers the anterior one-third of the eyeball. The respective portion of conjunctiva is referred to as the palpebral and bulbar conjunctiva. The conjunctiva is composed of two layers: an outer epithelium and its underlying stroma (substantia propria).

3. Cornea

The cornea is a strong clear bulge located at the front of the eye. Surface of the adult cornea has a radius of approximately 8mm. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens.

4. Aqueous Humor

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens.

5. Pupil

Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye. The size of the pupil (and therefore the amount of light that is admitted into the eye) is regulated by the pupillary reflex (also known as the "light reflex").

6. Iris

The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye. It is the coloured part of the eye (shades may vary individually like blue, green, brown, hazel, or grey).

7. Ciliary Muscle

The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humour into Schlemm's canal. The muscle has parasympathetic and sympathetic innervation. Contraction and relaxation of the ciliary muscle alters the curvature of



the lens. This process may be described simply as the balance existing at any time between two states: Ciliary Muscle relaxed (enables the eye to focus on distant objects) and Ciliary Muscle contracted (enables the eye to focus on near objects).

8. Lens

The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles.

9. Vitreous Humor

The vitreous humour (also known as the vitreous body) is located in the large area that occupies approximately 80% of each eye in the human body.

10. Retina

The retina is located at the back of the human eye. The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, lens, and finally the vitreous humour before reaching the retina.

11. Macula

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision.

12. Choroid

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina.

13. Optic Nerve

The optic nerve (a bundle of over 1 million nerve fibers) is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

Routes of Ocular Drug Delivery

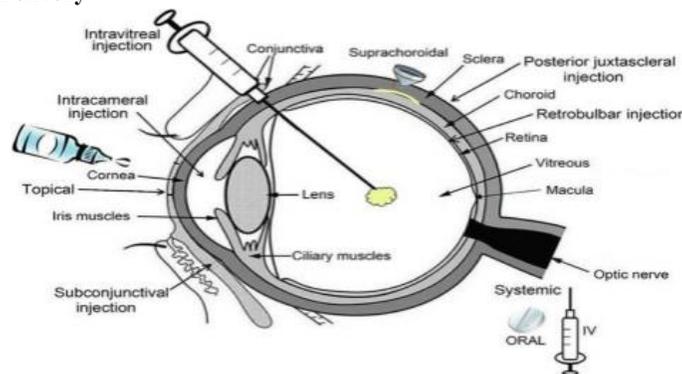


Figure 3. Routes of Ocular Drug Delivery

1. Intravitreal Route

In this route, the medication is delivered through injections in the vitreous humor of the eye. This route of administration is used to cure a number of eye disorders; the delivery through this ocular route is shown in Figure 3.

2. Intracameral Route

Anterior or posterior chambers of the eye are the sites of action for a drug in this route of administration. It can be demonstrated by injecting an anesthetic agent into the anterior chamber of the eye, usually during surgery.



3. Perilocular Route

The drug is administered around the eye in this route of administration. It can be explained by perilocular steroid injection involving the placement of steroids around the eye to treat intraocular inflammation or swelling [11].

4. Suprachoroidal Route

Supra choroid region of the eye is the target in this route of administration. The space existing between the sclera and the choroid is termed as suprachoroidal space.

5. Subconjunctival Route

In this route, the drug is administered to the mucus membrane, comprising of the open space of the eyeball and the inner surface of the eyelids.

6. Topical Route

Eye drops are the best examples of ophthalmic dosage forms used for topical administration of drugs in the eye as compared to ointments, gels and emulsions, which are used to cure the diseases of the anterior segment of the eye. It is the most convenient method of drug delivery to eye, due to ease of administration and lower cost.

Conventional Ocular Drug Delivery System

Topical drop instillation into the lower precorneal pocket is a patient compliant and widely recommended route of drug administration. However, most of the topically administered dose is lost due to reflex blinking and only 20% (~7 μ L) of instilled dose is retained in the precorneal pocket [12]. Concentration of drug available in the precorneal area acts as a driving force for its passive diffusion across cornea. However, for efficient ocular drug delivery with eye drops, high corneal permeation with longer drug cornea contact time is required. Several efforts have been made toward improving precorneal residence time and corneal penetration. To improve corneal permeation, iontophoresis, prodrugs, ion-pair forming agents and cyclodextrins are employed [13–15]. There is a wide range of ophthalmic products available in the market out of which around 70% of prescriptions include conventional eye drops. The reasons may be due to ease of bulk scale manufacturing, high patient acceptability, drug product efficacy, stability and cost effectiveness.

Topical Liquid/Solution Eye Drops

Topical drops are the most convenient, safe, immediately active, patient compliant and non-invasive mode of ocular drug administration. An eye drop solution provides a pulse drug permeation post topical drop instillation, after which its concentration rapidly declines. The kinetics of drug concentration decline may follow an approximate first order. Therefore, to improve drug contact time, permeation and ocular bioavailability; various additives may be added to topical eye drops such as viscosity enhancers, permeation enhancers and cyclodextrins. Viscosity enhancers improve precorneal residence time and bioavailability upon topical drop administration by enhancing formulation viscosity. Examples of viscosity enhancers include hydroxymethylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose and polyalcohol [16-18].

Among these approaches, viscosity enhancers and cyclodextrins suffer from the disadvantage of precorneal loss. In the case of penetration enhancers, care should be taken in the selection due to high sensitivity of ocular tissues. Hence, it leads to development of other conventional formulations approaches with inert carrier systems for ocular delivery of therapeutics. Conventional ocular formulations such as emulsions, suspensions, and ointments are developed to improve solubility, precorneal residence time and ocular bioavailability of drugs. In the current era of nanotechnology, these conventional formulations still retain their place, importance and capture the market at large. However, these formulations are associated with various side effects such as ocular irritation, redness, inflammation, vision interference and stability issues [19]. Currently, research is being conducted to improve in-vivo performance of these carrier systems and to minimize their side effects [20]. Several attempts are also being made to deliver drugs to posterior ocular tissues with conventional formulations.



Emulsions

An emulsion based formulation approach offers an advantage to improve both solubility and bioavailability of drugs. There are two types of emulsions which are commercially exploited as vehicles for active pharmaceuticals: oil in water (o/w) and water in oil (w/o) emulsion systems. For ophthalmic drug delivery, o/w emulsion is common and widely preferred over w/o system [21]. The reasons include less irritation and better ocular tolerance of o/w emulsion. Restasis™, Refresh Endura® (a non-medicated emulsion for eye lubrication) and AzaSite® are the examples of currently marketed ocular emulsions in the United States. Several studies have demonstrated applicability of emulsions in improving precorneal residence time, drug corneal permeation, providing sustained drug release and thereby enhancing ocular bioavailability.

Suspensions

Suspensions are another class of non-invasive ocular topical drop drug carrier systems. Suspension may be defined as dispersion of finely divided insoluble API in an aqueous solvent consisting of a suitable suspending and dispersing agent. In other words, the carrier solvent system is a saturated solution of API. Suspension particles retain in precorneal pocket and thereby improve drug contact time and duration of action relative to drug solution. Duration of drug action for suspension is particle size dependent. Smaller size particle replenishes the drug absorbed into ocular tissues from precorneal pocket. While on the other hand, larger particle size helps retain particles for longer time and slow drug dissolution [22]. Thus, an optimal particle size is expected to result in optimum drug activity.

Several suspension formulations are marketed worldwide to treat ocular bacterial infections. TobraDex® suspension is one of the widely recommended commercial products for subjects responding to steroid therapy. TobraDex® is a combination product of antibiotic, tobramycin (0.3%), and steroid, dexamethasone (0.1%). The major drawback of this commercial product is high viscosity. Recently, Scoper et al [23] made attempts to reduce the viscosity of TobraDex® and to improve its in vivo pharmacokinetics along with bactericidal activity. The rationale behind developing this formulation was to improve the suspension formulation characteristics such as quality, tear film kinetics and tissue permeation. The new suspension (TobraDex ST®) consists of tobramycin (0.3%), and steroid, dexamethasone (0.05%). Suspension settling studies showed that new form formulation had very low settling over 24h (3%) relative to marketed Tobra-Dex® (66%). Ocular distribution studies showed higher tissues concentrations of dexamethasone and tobramycin in rabbits treated with TobraDex ST® relative to Tobra-Dex®. New suspension formulation was found to be more effective than TobraDex® against Staphylococcus aureus and Pseudomonas aeruginosa. Clinical studies in human subjects showed high dexamethasone concentrations in aqueous humor than TobraDex®. These results suggest that new suspension formulation to be an alternative to marketed suspension, as it possesses better formulation characteristics, pharmacokinetics, bactericidal characteristic and patient compliance.

Contact Lens

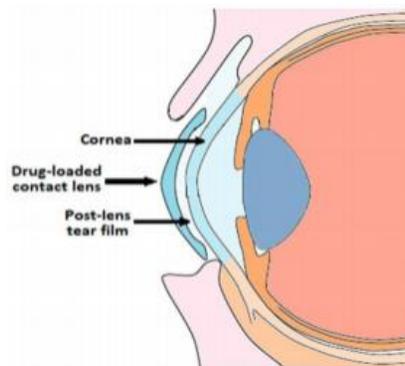


Figure 4. Ophthalmic Drug Delivery from Contact Lenses



Contact lenses are thin, and curved shape plastic disks which are designed to cover the cornea [32]. After application, contact lens adheres to the film of tears over the cornea due to the surface tension.

Drug loaded contact lens have been developed for ocular delivery of numerous drugs such as β blockers, antihistamines and antimicrobials. It is postulated that in presence of contact lens, drug molecules have longer residence time in the post-lens tear film which ultimately led to higher drug flux through cornea with less drug inflow into the nasolacrimal duct. Usually, drug is loaded into contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drug compared to conventional eye drops. Kim et al [36] observed much higher bioavailability of dexamethasone (DX) from poly(hydroxyethyl methacrylate) (PHEMA) contact lenses in comparison to eye drops. Indeed, efficient than topical drops, these soaked contact lenses suffers from disadvantages of inadequate drug loading and short term drug release.

To overcome these obstacles, particle-laden contact lenses and molecularly imprinted contact lenses have been developed. In particle-laden contact lenses, drug is first entrapped in vesicles such as liposomes, nanoparticles or microemulsion and then these vesicles are dispersed in the contact lens material. Gulsen et al [34] developed particle-laden contact lenses for ocular delivery of lidocaine. In two different studies, they have prepared particle laden contact lenses by dispersing lidocaine loaded microemulsion drops or liposome in poly-2-hydroxyethylmethacrylate (p-HEMA) hydrogels. Results of both the studies demonstrated the extended release of lidocaine over a period of 8 days.

It has been demonstrated that soft contact lenses fabricated by the molecular imprinting method have 1.6 times higher timolol loading capacity than the contact lenses prepared by a conventional method and also provided sustained timolol delivery [36]. In another study, ketotifen fumarate loaded imprinted lenses have revealed higher tear fluid bioavailability compared to drug soaked lenses or ketotifen fumarate marketed eye drops. The relative bioavailability for the imprinted lenses was 3 times greater than that of non-imprinted lenses. The AUC value of ketotifen fumarate for imprinted lenses, non-imprinted lenses and eye drops were $4365 \pm 1070 \mu\text{g/h}$ per milliliter, $493 \pm 180 \mu\text{g/h}$ per milliliter, $46.6 \pm 24.5 \mu\text{g/h}$ per milliliter, respectively [35]. The results clearly demonstrate more effectiveness of imprinted lenses over non-imprinted lenses and eye drops.

Implants

The aim of designing an intraocular implant is to prolong the activity of the drug, along with its controlled release by using a polymer or polymer system. An injectable delivery system of drug, like liposomes and nanoparticles, is easy to administer, but having limitation that after insertion, it becomes difficult to retract those particles during any complication, like toxic responses. So it is beneficial to use implants for balancing the rate and duration of drug release. Removal of ocular implants is easy and can be removed by surgical intervention [36].

Advantages of Ocular Drug Delivery System

They impart accuracy and uniformity in dosing rate. Pulsed dosing of conventional systems can be avoided.

Sustained and controlled release of drugs can be achieved.

By increasing corneal contact time, they cause enhancement in the ocular bioavailability of drugs and it is achieved by effective adherence of the drug to the corneal surface.

For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done.

They bypass the protective ophthalmic barriers, such as drainage, lacrimation and conjunctival absorption.

Disadvantages of Ophthalmic Drug Delivery Systems

The major drawbacks of ophthalmic drug delivery systems are as follows:

Short contact time of drug solution and eye surface.

Poor drug bioavailability.

Instability for dissolved drugs.

Potential patient discomfort.

Limited corneal permeability.



Challenges and Future Perspectives for Ocular Drug-Delivery Technologies

The shortcomings of the current ocular drug-delivery system, such as lower drug bioavailability for topically administered drugs and the invasive nature of posterior implants, create challenges, allowing novel technologies to rise with superior and effective treatment of ocular disorders. Ocular disorders such as cataract, dry eye disease, wet and dry AMD, glaucoma, DR, and DME are predicted to escalate in the next two decades. For a majority of the anterior segment disorders, eye drops are regarded as the safest and most convenient dosage form. Eye drops face the challenge of having low drug bioavailability at the target tissue. Controlled drug delivery with the help of nanoformulations such as nanomicelles, nanoparticles, liposomes, dendrimers, nanowafers, and microneedles can achieve high bioavailability of drugs at the anterior tissues, such as the conjunctiva and cornea. Currently, all treatments for back of the eye disorders are invasive in nature. Frequent intravitreal injections can lead to retinal detachment, hemorrhage, and discomfort to the patients. Design of a noninvasive sustained drug-delivery system for the posterior segment is challenging for ocular drug-delivery scientists. Thus, there is an urgent need for the development of novel noninvasive drug-delivery systems that can overcome ocular barriers, sustain drug release, and maintain effective drug levels at the back of the eye.

II. CONCLUSION

Drug delivery to targeted ocular tissues has been a major challenge to ocular scientists for decades. Administration of drug solutions as topical drops with conventional formulations was associated with certain drawbacks which initiated the introduction of different carrier systems for ocular delivery. Tremendous efforts are being put into ocular research toward the development of safe and patient-compliant novel drug delivery strategies. Currently, researchers are thriving hard to improve in-vivo performance of conventional formulations. On the other hand, advent of nanotechnology, new techniques, devices and their applications in drug delivery is developing immense interest to ocular scientists. Drug molecules are being encapsulated into nano-sized carrier systems or devices and are being delivered by invasive or non-invasive or minimally invasive mode of drug administration. Several nanotechnology based carrier systems are being developed and studied at large such as nanoparticles, liposomes, nanomicelles, nanosuspensions and dendrimers. Few of these are commercially manufactured at large scale and are applied clinically. Nanotechnology is benefiting the patient body by minimizing the drug induced toxicities and vision loss. Also, these nanocarriers or devices sustain drug release; improve specificity, when targeting moieties are used, and help to reduce the dosing frequency. However, there is still need of developing a carrier system which could reach targeted ocular tissue, including back of the eye tissues, post non-invasive mode of drug administration. With the current pace of ocular research and efforts being made and put in, it is expected to result in a topical drop formulation that retains high precorneal residence time, avoids non-specific drug tissue accumulation and deliver therapeutic drug levels into targeted ocular tissue (both anterior and posterior). In near future, this delivery system may replace invasive mode of drug administration to back of the eye such as periocular and intravitreal injection.

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