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CONTROLLED AND TARGATED DRUG DELIVERY SYSTEM FOR OCULUAR DISEASE

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ABSTRACT

The drug delivery is highly challenging due to the presence of anatomical and physiological barriers that limit drug absorption and therapeutic effectiveness. These barriers, classified as static (corneal epithelium, blood–ocular barrier) and dynamic (tear turnover, blinking, nasolacrimal drainage), significantly reduce drug bioavailability. As a result, conventional ocular dosage forms such as eye drops show poor drug retention and require frequent administration. The human eye possesses unique structural and functional characteristics that hinder drug penetration into targeted tissues. Although topical administration is the most convenient and patient-compliant route, especially for anterior segment diseases, it provides limited therapeutic concentrations for extended periods. More than 95% of marketed ophthalmic products are liquid formulations, yet their effectiveness is restricted by rapid precorneal elimination. To overcome these limitations, advanced drug delivery systems such as intravitreal implants, biodegradable and non-biodegradable polymeric systems, nanoparticles, in situ gels, and viscosity-enhanced formulations have been developed. These systems aim to prolong drug residence time, provide controlled and sustained release, reduce dosing frequency, and improve patient compliance. Recent advancements focus on enhancing ocular permeation and achieving targeted drug delivery, thereby improving therapeutic outcomes in chronic ocular diseases.

INTRODUCTION

The human eye is a highly specialized organ with a complex anatomical and physiological structure that presents significant challenges for drug delivery. Its sophisticated protective mechanisms are designed to prevent the entry of foreign substances and maintain ocular homeostasis. While these barriers are essential for preserving vision, they also limit the effectiveness of therapeutic agents. Conventional ocular drug delivery systems, particularly eye drops, suffer from rapid precorneal elimination, resulting in poor drug bioavailability. Only a small fraction of the administered dose penetrates the corneal layer and reaches the internal ocular tissues, making effective treatment difficult [1]. Ocular drug delivery systems are broadly categorized based on their target regions: the anterior segment and the posterior segment of the eye. Conventional dosage forms such as eye drops, suspensions, and ointments are commonly used for treating diseases of the anterior segment. However, these formulations often fail to provide optimal therapeutic outcomes because a substantial portion of the drug is rapidly removed through blinking, tear turnover, and nasolacrimal drainage. Consequently, only a small amount of the drug reaches the desired site of action, requiring frequent administration to maintain therapeutic concentrations [2]. The posterior segment of the eye includes the retina, vitreous humour, and choroid. Diseases affecting these tissues, such as age-related macular degeneration, diabetic retinopathy, and retinal disorders, are often vision-threatening and require advanced delivery strategies. Conventional topical formulations are generally ineffective in delivering drugs to the posterior segment because of the numerous ocular barriers. Therefore, systemic administration, periocular injections, intravitreal injections, and implantable drug delivery systems are commonly employed to achieve therapeutic drug concentrations in these tissues [3]. The eye possesses several anatomical and physiological barriers that restrict drug penetration. These include the corneal epithelium, conjunctival barriers, blood-aqueous barrier, and blood-retinal barrier. Regardless of the route of administration-whether topical,

subconjunctival, sub-tenon, periocular, or intravitreal-therapeutic agents must overcome these barriers to reach their target tissues. For anterior segment disorders involving the cornea, conjunctiva, sclera, and anterior iris, topical eye drops remain the most widely used treatment option. However, an instilled eye drop is typically cleared from the ocular surface within 5–6 minutes, and only about 1–3% of the administered dose reaches intraocular tissues [4]. Similar studies have reported that only a limited percentage of topically applied drugs successfully penetrate the eye and achieve therapeutic levels [5]. To overcome these limitations, various formulation approaches have been developed to enhance ocular residence time and improve bioavailability. These include viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts that prolong contact between the drug and the ocular surface [6]. Despite these advancements, most topical formulations remain ineffective for treating diseases of the posterior segment. As a result, systemic therapies and intraocular injections continue to be widely used in clinical practice [7]. Long-term management of chronic ocular diseases such as glaucoma, uveitis, macular edema, age-related macular degeneration, and retinitis pigmentosa remains challenging. Poor patient adherence to treatment regimens is a major concern, with studies indicating that nearly half of glaucoma patients discontinue topical therapy within six months [8]. Additionally, repeated intravitreal injections may cause serious complications, including retinal detachment and endophthalmitis. Therefore, the development of advanced ocular drug delivery systems capable of sustained, targeted, and controlled drug release is essential to improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance.treatment burden, and enhance patient compliance.

1. ANOTOMY AND PHYSIOLOGY OF THE EYE

Anatomy And Function of Eye The eye is basically a globe suspended in the ocular orbit that is designed to concentrate, transmit, and detect incoming light.

1.1 Sclera

Sclera Collagen fibres and proteoglycans are embedded in an extracellular matrix, specifically in the sclera. Scleral permeability is dependent on the molecular radius and kind of goes away as the molecular radius increases. In contrast to the anterior sclera, the posterior sclera has a looser weave of collagen fibres [9].The human selera is especially thick around the limbus (0.53 + 0.14 mm), thin on the equator (0.39 + 0.17 mm), and significantly thicker near the optic nerve (0.9-1.0 mm). The medication molecule's permeability through the sclera may also be influenced by its cost. Because positively charged capsules connect to the negatively charged proteoglycan matrix, they may also exhibit extremely poor permeability. It is a spherical structure with a wall consisting of three layers.

- Outer sclera
- Middle choroids layer
- The inner retina

The sclera mainly consists of collagen fibers and proteoglycans embedded in an extracellular matrix [10]. Scleral permeability has been shown to have a strong dependence on the molecular radius; scleral permeability decreases roughly exponentially with molecular radius [11]. Additionally, the posterior sclera is composed of a looser weave of collagen fibers than the anterior sclera [12].and the human sclera is relatively thick near the limbus (0.53 ± 0.14 mm), thin at the equator (0.39 ± 0.17 mm), and much thicker near the optic nerve (0.9–1.0 mm). Thus, the ideal location for transscleral drug delivery is near the equator at 12–17 mm posterior to the corneoscleral limbus [13]. Hydrophobicity of drugs affects scleral permeability; increase of lipophilicity shows lower permeability; and hydrophilic drugs may diffuse through the aqueous medium of proteoglycans in the fibre matrix pores more easily than lipophilic drugs.

1.2 Conjunctiva

Conjunctiva The conjunctiva is responsible for maintaining and repairing the precorneal tear film in addition to shielding the eyes. The thin, visible membrane known as the conjunctiva is located on the inner surface of the eyelids and is visible on the outside of the globe. The substantia propria, which is highly vascularized, submucosa, and epithelium are the building blocks of the conjunctiva. The bulbar epithelium is composed of five to seven movable layers. The form now resembles a palisade rather than a pavement due to the tight connections between the corneal epithelial cells, which make the conjunctiva extremely impermeable.

1.3 Choroid

Choroid The choroid layer, which is situated behind the retina, feeds the outer regions of the retina and absorbs excess radiation. This thin, somewhat vascular membrane is made up of blood vessels. The choroid has one of the body's greatest blood flow rates. Through the lamina fuse, the choroid is a weakly attached structure to the interior floor of the sclera.

1.4 Retina

The human retina is located behind the eye. The "display" that an image is formed on due to light that has gone through the cornea, aqueous humour, pupil, lens, and vitreous humour before reaching the retina is known as the retina. As such, the retinal "display" is a slightly sensitive form that lines the inside of the eye. It is made up of photosensitive cells called rods and cones, as well as the nerve fibers that connect them. These cells translate light into nerve impulses, which are then transmitted to the brain via the optic nerve.

1.5 Iris

The lens is a transparent form contained in a conspicuous, thin capsule. It is positioned behind the attention-deficit student and encompassed by the cillary muscles. Light passing through the attention is helped to refract (first refracted through the cornea). At the retina, the lens concentrates light into an image.

Lodging is the term for the form-adjusting process of the lens, which is accomplished by contracting and relaxing the ciliary muscles.

1.6 Optic nerve

Nerve signals are transmitted from the attention to the brain by the optic nerve, a bundle of more than a million nerve fibers. These nerve markers consist of information on a picture that the brain can process. The optic disk is the portion of the optic nerve visible at the retina that is located on the front floor.

1.7 Pupil

The amount of light that is allowed into the attention is controlled by a black orifice located inside the iris. The pupil is typically perceived as the darker "centre" of attention, but it may actually be more accurately defined as the circular opening in the iris's center through which light enters the attention.

1.8 Cornea

Cornea The clear, noticeable protrusion in the cornea at the front of the attention that sends images back to the scared system. The adult cornea has a radius of roughly 7-8 mm, which makes up about one-sixth of the entire floor area of the attention ball. The epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium are the five layers that make up the cornea. This is a crucial route for drugs to enter the eye. The epithelium is composed of five layers, or 10^-6 cells. Within the cornea, the thickness ranges from 0.5 to 0.7 mm.There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue.The various possible routes for ocular drug delivery are described below: Periocular and Intraocular Injections

2. OCULAR DRUG DELIVERY SYSTEM

The major challenge faced by today's pharmacologist and formulation scientist is ocular drug delivery. Topical eye drop is 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 longer duration in target tissues. In the past two decades, ocular drug delivery research acceleratedly 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 tissue [14]. Also, recent developments with other ocular drug delivery strategies employing in situ gels, implants, contact lens and microneedles have been discussed

3.BARRIERS FOR OCULAR DRUG DELIVERY

Ocular drug delivery suffers from the following barrier effects:

- 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.
- For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done..
- Systemic and visual side effects are lower and absorption is faster.

3.1 Barriers to Restrict Intraocular Drug Transport

• Tear

One of the precorneal barriers is tear film which reduces the effective concentration of the administrated drugs due to dilution by the tear turnover (approximately 1 μL/min), accelerated clearance, and binding of the drug molecule to the tear proteins. In addition, the dosing volume of instillation is usually 20–50 μL whereas the size of cul-de-sac is only 7–10 μL. The excess volume may spill out on the cheek or exit through the nasolacrimal duct [11-14]. For details of structure and function of tear film see.

• Cornea

The cornea consists of three layers; epithelium, stroma and endothelium, and a mechanical barrier to inhibit transport of exogenous substances into the eye [15]. Each layer possesses a different polarity and a rate-limiting structure for drug permeation. The corneal epithelium is of a lipophilic nature, and tight junctions among cells are formed to restrict paracellular drug permeation from the tear film. The stroma is composed of an extracellular matrix of a lamellar arrangement of collagen fibrils.

3.2 Conjunctiva

Conjunctiva of the eyelids and globe is a thin and transparent membrane, which is involved in the formation and maintenance of the tear film. In addition, conjunctiva or episclera has a rich supply of capillaries and lymphatics.therefore, administrated drugs in the conjunctival or episcleral space may be cleared through blood and lymph.The conjunctival blood vessels do not form the conjunctival lymphatics act as an efflux system for the efficient elimination from the conjunctival space.

3.3 Lacrimal fluid-eye barriers

Absorption of the drug from the lacrimal fluid can be limited by the corneal epithelium present in the eye. Lipophilic drugs show higher permeability in the cornea as compared to hydrophilic drugs.

4. ROUTES OF OCULAR DRUG DELIVERY SYSTEM

inadequacy of topical and systemic administration in providing therapeutic drug concentrations to the posterior segment, the periocular and intraocular routes of administration are now being utilized. The most popular and generally advised method of administering medication for posterior ocular illnesses is intravitreal injection, which can also be a useful means of delivering high therapeutic doses. However, it can result in low patient compliance and an increased risk of problems such endophthalmitis, ocular hypertension, cataracts, vitreous hemorrhage, and even retinal detachment because of the frequent requirement for very intrusive injections to maintain therapeutic levels.

4.1 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.
4.2 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 aesthetic agent into the anterior chamber of the eye, usually during surgery.
4.3 Periocular route
The drug is administered around the eye in this route of administration. It can be explained by peril ocular steroid injection involving the placement of steroids around the eye to treat intraocular inflammation or swelling.
4.4 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.
4.5 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.

5. TYPES OF OCULAR DRUG DELIBVERY SYSTEM

1. Topical Delivery Systems
   - - Eye drops, Ointments, Gels, Suspensions
2. Injectable Delivery Systems
   - - Intravitreal injections, Subconjunctival injections, Intraocular implants
3. Implantable Delivery Systems
   - Intraocular implants, Episcleral implants
   - Scleral implants
4. Nanoparticle-Based Delivery Systems
   - Liposomes, Nanoparticles, Dendrimers
5. Controlled Release Delivery Systems
   - Sustained release systems, Extended-release systems, Delayed release systems

6. RECENT ADVANCE IN OCULAR DRUG DELIVERY

On the other hand, direct intravitreal implants, using biodegradable or non-biodegradable polymer technology, have been widely investigated for the treatment of chronic vitreoretinal diseases. There is urgent need to develop ocular drug delivery systems which provide controlled release for the treatment of chronic diseases and increase patient's and doctor's convenience to reduce the dosing frequency and invasive treatment. In this article, progress increase ocular bioavailability and prolong the retention time on the ocular surface, numerous ophthalmic vehicles such as viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts, have been investigated for topical application to the eyes of ocular drug delivery systems under clinical trials and in late experimental stage is reviewed.

7. CLINICLE APPLICATIONS

- Travoprost eyedrops for glaucoma management
- Travoprost eyedrops for glaucoma management
- Ranibizumab intravitreal injections for AMD treatment
- Bevacizumab intravitreal injections for AMD management Diabetic Retinopathy
- Cyclosporine eyedrops for uveitis management Dry Eye Syndrome
- Cyclosporine eyedrops for dry eye treatment

8. ADVANTAGES OF OCULAR DRUG DELIVERY

a. For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done Sustained and controlled release of drugs can be achieved.
b. They provide better housing of delivery systems.
c. To Enhanced Patient Compliance: Convenient and easy-to-use delivery systems
d. Increased Efficacy: Higher therapeutic effectiveness due to sustained drug release

9. DISADVANTAGES OF OCULAR DRUG DELIVERY

- Short contact time of drug solution and eye surface.
- Poor bioavailability.
- Instability for dissolved drugs.
- It can show instability of the dissolved drug
- Preservatives must be used.
- The drug solution is the stays a very small period on the eye surface
- They can interfere with the vision

10. CHALLENGES AND LIMITATIONS OF OCULAR DRUG DELIVERY SYSTEM

Challenges in ocular drug delivery systems are to design a therapeutic system which can provide an optimal concentration of a drug at the target region and with high therapeutic efficacy.The challenges in ocular drug delivery systems are categorized as follows
10.1 Anterior segment delivery challenges
Topical formulations are mostly preferred over systemic formulations in the ocular delivery system because if any drug formulation is administered to eye, before reaching the anatomical barrier of the cornea, the drug molecule has to face the precorneal barriers, the tear film and conjunctiva, which come first in the pathway and slow the penetration of the active moiety in the eye.
10.2 Posterior segment delivery challenges
BRB inhibits the entry of topically applied ocular drugs at the posterior segment of eye. Delivery of drugs is inhibited by some factors at the posterior segment of ocular tissue and this effect is also responsible for poor

ocular bioavailability. The BRB is responsible for limiting the effect of the intravenous route at the posterior site for drug delivery (24).and it also limits the entry of the systemically administered drug in the retina.

11. FUTURE STRATEGES OF OCULAR DRUG DELIVERY SYSTEM

Nanotechnology based ocular drug deliveryMany methods have been used in the last few decades to cure illnesses of the eyes. One strategy being investigated for drug distribution to the front and posterior segments of the eye is the use of nanotechnology in ocular formulations. s. It is possible to create nanotechnology-based solutions with the right particle size to guarantee minimal eye tissue irritation, sufficient bioavailability, and compatibility. To delivering drugs to the eyes, several nanocarriers have been created, including liposomes, nanoparticles, nanosuspensions, nano micelles, and dendrimers. In terms of enhancing ocular bioavailability, a few of them have demonstrated encouraging outcomes.

11.1 Nano micelles

Nano micelles are the most used carrier systems to formulate therapeutic agents into clear aqueous solutions. In general, these nano micelles are made with amphiphilic molecules. These molecules may be surfactant or polymeric in nature. Recently, Cholkar et al have reviewed in detail about ocular barriers and application of nano micelles-based technology in ocular drug delivery.Drug-Eluting Contact Lenses: Silicone hydrogel lenses are being developed to deliver drugs directly to the eye over several days, potentially replacing drops for post- surgical care and chronic conditions.

12. CONCLUSION

Ocular drug delivery systems have undergone significant transformations in recent years, aiming to overcome the challenges associated with conventional eye drop formulations. The emergence of novel drug delivery technologies has improved the efficacy, safety, and patient compliance of ocular therapeutics. This review has highlighted the advancements in ocular drug delivery systems, including nanoparticles, liposomes, microspheres, hydrogels, and implants.

13. AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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The authors have no conflicts of interest to declare.

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17. REFERENCE

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