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(REVIEW ARTICLE)

Ocular drug delivery systems: A comprehensive review of innovative formulations, challenges and opportunities

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Abstract

The human eye's complex anatomy and physiology pose significant challenges to effective ocular drug delivery. This comprehensive review explores the eye's structure, ocular disorders such as cataracts, conjunctivitis, glaucoma, and fungal keratitis, and various ocular drug delivery systems. The review discusses the advantages and disadvantages of ocular drug delivery systems, including topical administration, intravitreal injection, subconjunctival routes, and implantable devices. Novel formulations such as nanosuspensions, microemulsions, liposomes, and niosomes are examined for their potential to overcome anatomical limitations and enhance bioavailability. The mechanisms of drug release, including diffusion, osmosis, and bio-erosion, are also discussed. Furthermore, the review highlights the importance of targeting specific ocular tissues and overcoming defensive mechanisms to achieve optimal therapeutic efficacy.

Keywords: Ocular drug delivery; Ocular disorders; Nanoparticle-based delivery systems; Controlled release formulations; Blood-retinal barrier

1. Introduction

The human eye is one of the most easily accessible organs for drug administration, effective ocular delivery maintains a goal that yet to be fulfilled. The potential explanations are in the anatomical and physiological features of the eyeball and its protective systems, with the technical qualities of ocular formulations (1). The human eye is a complex sensory organ characterized by challenging physiology and anatomy. It is divided into two parts, its front and the back, which are interconnected and linked to other sensory organs via a network of nerves. As a sensory organ, the eye is kept secure by several functional and structural defensive barriers (2). It is necessary to concentrate while designing for targeting the eye because it is a very sensitive and Byzantine component with many anatomical and physiological obstacles (3). For pharmaceutical researchers, ocular administration of drugs remains as one of the most difficult tasks. The distinctive anatomy of the eye limits the penetration of pharmaceutical compounds to the targeted location of action. Ocular drug delivery can be categorized into anterior and posterior portions (4).

The ophthalmic administration of drugs compounds has been an essential challenge to pharmacologists and drug delivery experts. This is because the eye has a special anatomy and physiology (6). The most important goals of any ocular drug-delivery system are to sustain therapeutic drug concentrations at the target location, minimize dosing frequency, and overcoming numerous dynamic and static ocular obstacles (7). The eye's anatomy challenges the administration of therapeutic medications. The blood-retinal barrier (BRB) renders the eye resistant to foreign compounds and drug substances attempting to enter the targeted ocular tissues (8). Ocular drug delivery devices (ODD)

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provide a viable solution to the challenge of inadequate adherence to self-administration of topical glaucoma medicines (9). As a sensory organ, the eye is one of the most important organs in the body because it uses the optic nerve to send visual information to the brain (10). The physiological obstacles the eyes possess make it difficult to transfer drugs through the eyes. These include corneal impermeability, nasolacrimal discharge, blinking, and tear washout (11). This can be accomplished by injecting medications intraocularly, orally, parenterally, or by a combination of these methods (12). Hyaluronic acid is a key constituent of the aqueous and transparent fluids of the eye (13).

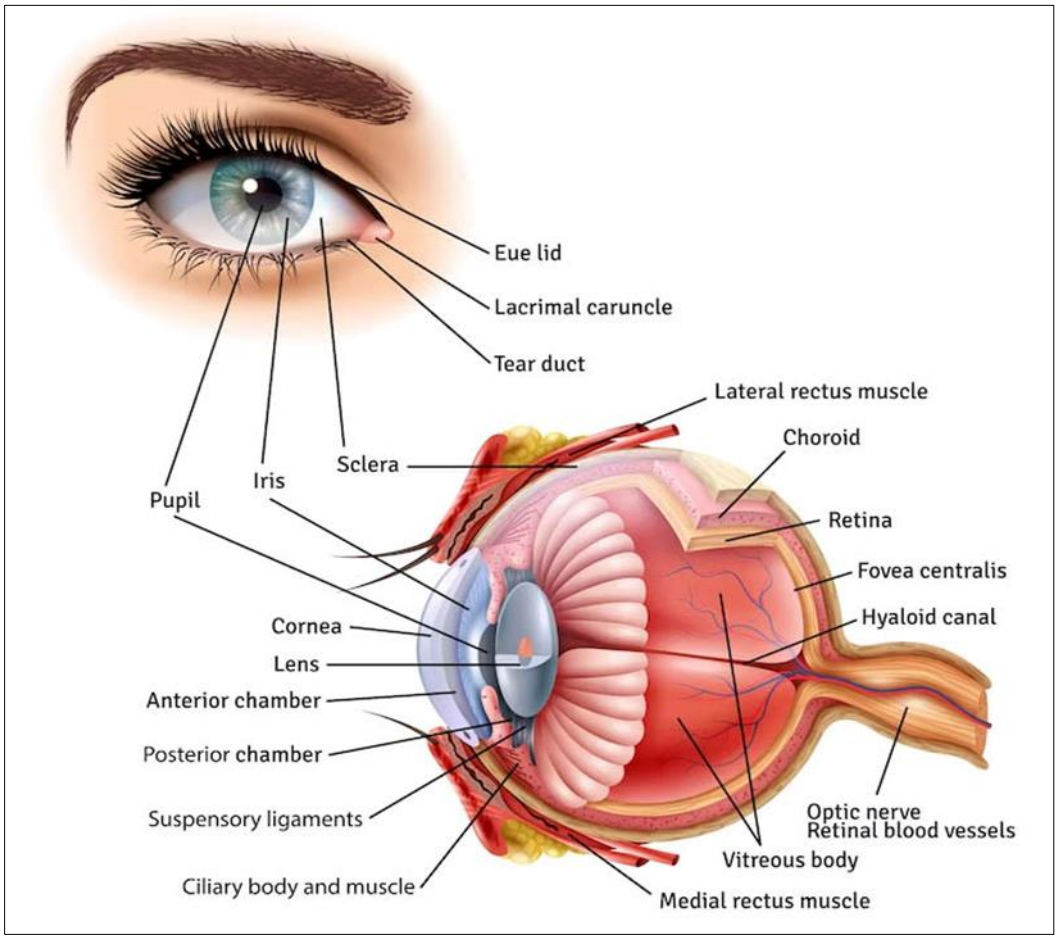

Figure 1 Structure of the Eye (5)

2. Anatomy of the eye

The human eye is an exceptionally sensitive and intricate organ. (Figure 2) displays the anatomy of the human eye, which consists of anterior and posterior divisions. The cornea, pupil, lens, ciliary body, and tear film make up the anterior section. The conjunctiva, choroid, retina, vitreous humor, optic nerve, and sclera make up the posterior section. The composition and volume of tears are regulated by orbital glands and epithelial secretions. The cornea is the anterior segment of the eye that transmits and refracts light into the ocular cavity. It is categorized into epithelium, stroma, and endothelium. The epithelium consists of five to seven layers of tightly interconnected cells. Stroma is a compact, aqueous layer. The endothelium maintains the cornea's transparency (14). The iris is the pigmented part of the eye that regulates the amount of light entering the eye. The dark central aperture within the iris is referred to as the pupil. The pupil adjusts its diameter in response to the surrounding light levels. The lens is the translucent structure that concentrates light onto the retina. The ciliary body consists of pigmented and non-pigmented ciliary epithelia, stroma, and ciliary muscles. The capillaries of the ciliary body facilitate communication between the anterior and posterior regions (15).

The vitreous humor is a gel-like, transparent, avascular connective tissue located between the eye lens and the retina. It is composed 99.9% water, hyaluronic acid, ions, and collagen. The conjunctiva is a fragile, translucent membrane that lines the inner surface of the eyelids and covers the anterior aspect of the sclera. It is a mucous membrane consisting of three layers: an exterior epithelium, a substantia propria which includes nerves, lymphatic vessels, and blood vessels, and a submucosa layer connected to the sclera. The sclera is a continuation of the cornea. It consists of collagen and

mucopolysaccharides. The circulatory layer known as the choroid lies between the sclera and the retina. The retina is a thin layer of tissue consisting of neural and glial cells that lines the posterior aspect of the eye. It generates electrical impulses that go to the brain via the optic nerve (15).

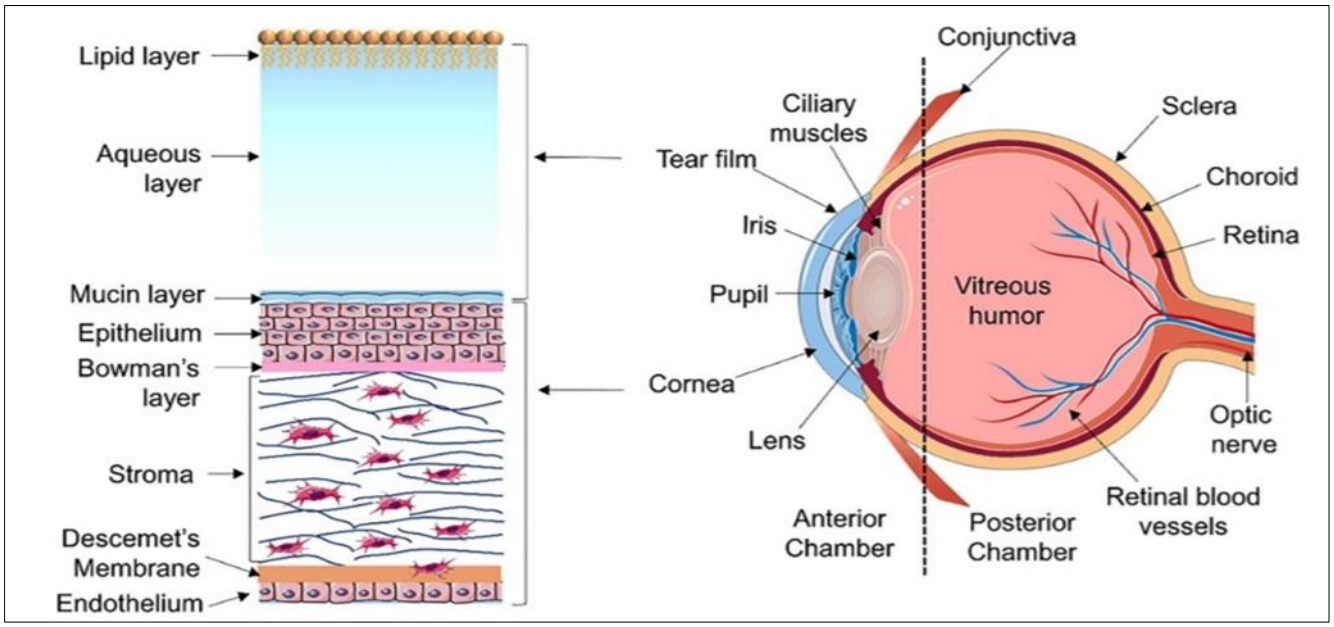

Figure 2 Anatomy of the Eye (14)

3. Ocular Disorders

3.1. Cataract

Around the world, 40–60% of blindness is caused by cataracts. Crystalline proteins make the lens translucent and categorize cataracts as cortical, nuclear, or posterior subcapsular. According to the National Programme for Control of Blindness and Visual Impairment, cataracts account for 62.6% of preventable blindness in India and can be brought on by smoking, sunlight, diabetes, malnutrition, and genetic predisposition. Cataracts are associated with alterations in α, β, and crystalline proteins and their corresponding genes (16).

3.2. Conjunctivitis

The conjunctivitis affects people of all ages, ethnicities, and identities. It results in conjunctival edema and may be either infectious or non-infectious. Microbial infections result in infectious conjunctivitis, whereas irritants and allergens lead to non-infectious conjunctivitis. Conjunctivitis results in erythema, irritation, excessive tearing, and ocular secretions. 40% of the global population suffers from allergic conjunctivitis. Topical antibiotics or anti-inflammatories can be utilized to treat conjunctivitis (16). An inflammation of the conjunctiva that may result from bacterial and viral infections, pollen and other allergens, tobacco, and pollution (17).

3.3. Fungal keratitis

Fungal keratitis occurs in traumatized corneas but not in healthy corneas. It can be caused by Candida tropicalis, Albicans, Krusei, Glabrata, and Parapsilosis. Forty percent of infectious keratitis cases arise in underdeveloped countries. Risk factors for this disease include contact lenses, trauma, ocular surgery, corticosteroids, diabetes, leprosy, and HIV infection (16). A corneal inflammation brought on by a fungal, viral, or bacterial infection. Additional disorders encompass the ocular consequences of rosacea, blepharitis (inflammation of the eyelid margins), and chalazia (Meibomian cysts of the eyelid) (17).

3.4. Glaucoma

The accumulation of pressure in the anterior and posterior chambers of the choroid layer resulting from inadequate drainage of the aqueous humor (18).

4. Ocular drug delivery systems

The essential characteristics of an ideal controlled-release ocular drugs delivery system are it must not elicit a foreign-body feeling or prolonged visual blurring. It should have greater local activity than systemic effects. It must provide the medicine to the appropriate location, specifically targeting the ciliary body. It must be simple to self-administer. The daily administration frequency should be decreased. The main strategies in the design of controlled-release ocular medication delivery systems aim to reduce the removal of the drug through tear flow. The different formulations will be described as follows (18).

4.1. Ophthalmic Formulations of Drug Resinates

The first successful controlled-release ocular formulation for topical use with ion exchange resin technology for glaucoma therapy was betaxolol ionic suspension (Betoptic S, 0.25%). The medication is attached to Amberlite resin, a cationic exchange resin composed of a sulfonic acid styrene-vinyl copolymer. The formulation contains carbomer (Carbopol 934P), which functions as a viscosity enhancer, hence prolonging the product's residence period in the eye [19].

4.2. Viscous Solutions and Hydrogels

Hydrogel is made up of three-dimensional, hydrophilic networks of polymers that can hold a large amount of water or biological fluids (20). The mechanism behind the formation of viscous solutions and hydrogels is the incorporation of hydrocolloids into aqueous medicinal solutions. Frequently utilized polymers in these formulations include cellulose derivatives, carbomers, polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone, and more recently, hyaluronic acid. Gels provide an extended residence duration in the pre-corneal region compared to viscous solutions (21). Gels are administered directly to the eye to provide local action (22). Consequently, the medication solution that forms a gel in the conjunctival cul-de-sac is more tolerable. Consequently, these formulations are designated as in-situ gel-forming systems [21].

4.3. Mucoadhesive Formulations

Entanglement of non-covalent bonds between polymers and mucous is the basis for mucoadhesion. Frequently utilized polymers in these formulations include various high molecular weight polymers including diverse functional groups such as carboxyl, hydroxyl, amino, and sulphate, which may form hydrogen bonds and cannot permeate biological membranes. These have been evaluated as potential mucoadhesive excipients in ocular administration systems (18).

5. Different nano-formulations employed for ocular delivery

5.1. Nanosuspensions

The construction of nano-formulations is intended to be modified to get the required medication concentration at the target region, despite overcoming anatomical limitations. (23) Nanosuspension is made up of pure medication particles dispersed in water (24). Nano drug delivery systems can maintain drug release and avoid drug degradation resulting in great potential to improve drug therapy (25). Nanosuspensions are designed for medications that demonstrate inadequate solubility in the dispersion medium. The drug's kinetic profile can be enhanced, leading to better bioavailability, if designed as nanosuspensions. Surfactants are employed to enhance the stability of scattered systems. Nanosuspensions are beneficial not only for their adhesion to ocular surfaces but also for hydrophobic active pharmaceutical ingredients (APIs) that exhibit reduced solubility in lacrimal fluid, hence enhancing drug release (23,26).

5.2. Micro/ Nano emulsions

These are clear emulsions composed of oil and water that are thermodynamically stable, with their stability altered via the use of surfactants or cosurfactants, which function by lowering the interfacial tension at the boundary of the two phases. The inclusion of cosurfactants enhances medication loading efficiency and drug disintegration. Microemulsions significantly influence ocular delivery formulations due to their capacity to penetrate ocular barriers, and they can be effectively utilized as penetration modifiers.

Increased drug penetration allows the substance to reach the intended target, facilitating the beginning of action while significantly minimizing drug loss. Micro- or nano-formulations enhance the contact duration of an ocular preparation on the corneal epithelial surface (27,28).

5.3. Polymer-based nanoparticles

Nanoparticles derived from polymers Nanoparticles utilized in ocular formulations consist of particles with a diameter less than 1 mm; ideally, this dimension ranges from 10 to 1000 nm, offering many benefits, including prolonged retention at ocular regions (29). Ophthalmic medicines exhibit an extended residence time in nanogel systems using muco-adhesive polymers such as chitosan. Functionalized polymer-based nanogels are an excellent approach for ocular delivery as they allow for surface modification to control the release kinetics of encapsulated medications, enhance bioavailability, improve corneal penetration, and target specific anatomical areas within the eye (30). The polymers include natural substances such as Gelatin, Sodium Alginate, and Chitosan, as well as biodegradable polymers like Polylactides, Polycaprolactone, and Poly(lactic-co-glycolic acid). In recent decades, nanoparticles have been a subject of investigation due to their sustained, site-specific effect without affecting non-target tissues (29).

Figure 3 Mechanism of Action of Brinzolamide Nanoparticles (29)

5.4. Liposomes

Liposomes are widely used nanocarriers for ophthalmic formulations, characterized by their bilayered phospholipid membrane, typically derived from cholesterol (29). Developments in liposomal formulations have made it easier to develop promising antibiotic delivery methods that could help with significant issues in the treatment of infectious diseases. Liposomal encapsulation improves the stability and safety of antibiotics (31). They can encapsulate both hydrophobic and hydrophilic drugs, with the capacity to enclose hydrophilic drugs in their core while enveloping lipophilic drugs externally (32). It not only decreases the frequency of dosage administration but also demonstrates that cationic liposomes display a greater degree of adhesion at the negatively charged corneal position due to electrostatic attraction. The liposomes demonstrate the capacity to merge with the plasma membrane, facilitating the exchange of their phospholipid components with those of the cell membrane and influencing the retention of medicines at the target position (Fig. 4).

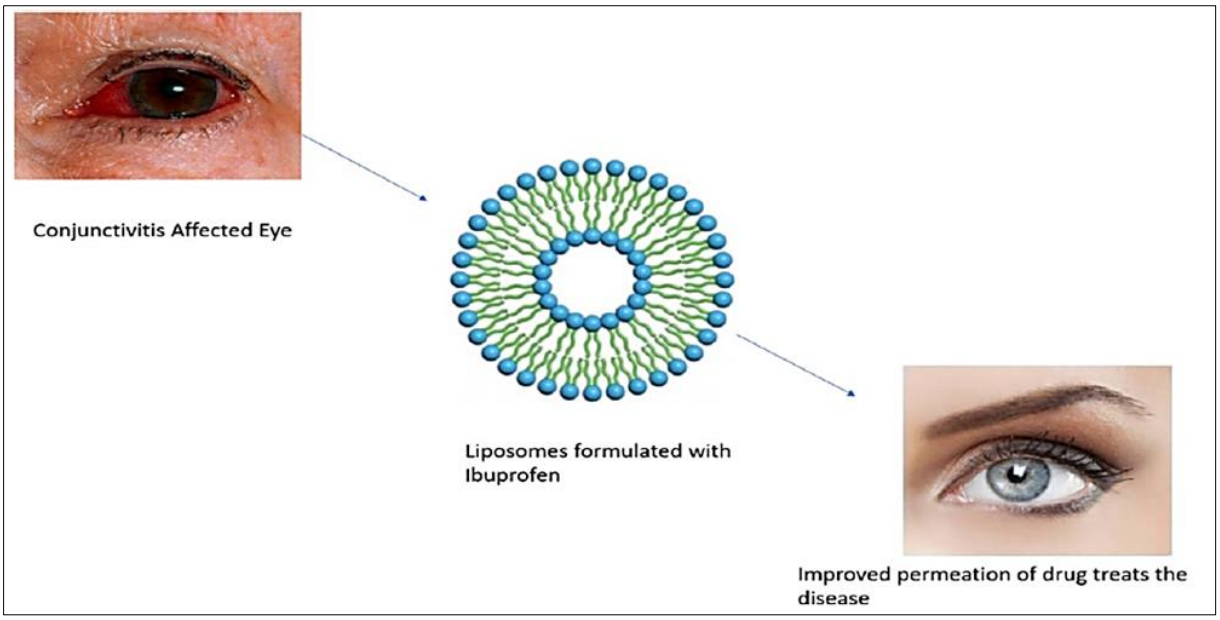

Figure 4 Treatment of conjunctivitis with liposomes (29)

5.5. Niosomes

Niosomes are aqueous phase bilayer-structured vesicles composed of amphiphilic non-ionic surfactants that vary in size from 10 nm to more than 5 μm (29). Niosomes have the ability to increase drug bioavailability by reducing intraocular pressure. In ophthalmic preparation, achieving the necessary bioavailability of the drugs is a simple process (33).

6. Mechanism of drug release (34)

The mechanism of controlled drug release into the eye is as follows:

- Diffusion
- Osmosis
- Bio-erosion

6.1. Diffusion

The medicine is continually delivered into the tear fluid across the membrane at a controlled speed in the diffusion process. If the insert consists of a solid, non-erodible matrix containing pores and a distributed medication. The drug release may occur by diffusion via the pores. The controlled release can be further modulated by the progressive dissolving of the solid distributed drug inside this matrix due to the inward diffusion of aqueous solutions.

6.2. Osmosis

The Osmosis mechanism involves an insert which include a transverse impermeable elastic membrane that separates the insert into two compartments. The first compartment is enclosed by a semi-permeable membrane and the impermeable elastic membrane, while the second compartment is delineated by an impermeable membrane, serving as a reservoir for the drug, which is in liquid or gel form. Upon insertion into the liquid-filled cavity of the eye, water permeates the first compartment, causing the elastic membrane to distend, therefore enlarging the first compartment and compressing the second compartment, which propels the medication through the release hole.

6.3. Bioerosion

The bio-erosion technique involves a configuration of the insert's body composed of a matrix of bio-erodible material containing distributed medication. The interaction between the insert and tear fluid leads to a regulated, persistent release of the medicine through the bioerosion of the matrix. The medication may be evenly distributed inside the matrix; however, a better controlled release is thought to be achieved if the drug is concentrated near the surface of the matrix.

7. Function of the eye (35,36)

- **Sclera-** the eye's white outer protective layer, also referred to as the "white of the eye."
- **Cornea -** the transparent, convex structure located in the anterior segment of the eye.
- **Iris-** which is visible through the cornea, is the colored portion of the eye that might be blue, brown, green, gray, etc.
- **Pupil-** the central black portion of the eye, situated within the iris. It constricts or expands in response to the intensity of light transmitted through it.
- **Lens -** the transparent, biconvex disk situated directly posterior to the iris and pupil.
- **Aqueous humour-** The translucent fluid, like water in substance, that circulates below the cornea and in front of the lens.
- **Vitreous humour -** The translucent gelatinous substance that occupies the space within the eyeball between the lens and the retina.
- **Retina -** The light-sensitive layer composed of millions of nerve cells that lines the posterior segment of the eyeball. The cells are categorized into two primary categories, known as rods and cones, based on their microscopic morphology.
- **Rods-** They are more common, dispersed across the retina, with a greater concentration on the outer border, and react to low light levels.
- **Cones-** Much smaller, located in the center of the retina, they react to color and details.
- **Macula-** The retina's tiny core, which oversees reading vision.

- **Retinal pigment epithelium -** This is a pigmented cellular layer located in the posterior aspect of the retina, tasked with supplying oxygen and essential nutrients to the rods and cones.
- **Choroid-** The vast network of blood arteries that supply the retinal pigment cells with nutrition and oxygen.
- **Optic disc-** A tiny, oval, yellow structure in the retina to which all rods and cones send nerve cell connections.
- **Optic nerve and its branches -** The bundle of neuronal connections that transmits signals from the eyeball to various regions of the brain.

8. The advantages of ocular drug delivery systems (37,38)

- Enhanced precision in dosage. To mitigate the adverse effects of pulsed dosing generated by traditional techniques.
- To provide sustained, controlled medication administration.
- To enhance the ocular bioavailability of the medicine by prolonging the corneal contact duration. This can be accomplished by good adhesion to the corneal surface.
- To offer targeting inside the eye's globe to stop damage to other eye tissues.
- To bypass defensive mechanisms, like as drainage, lacrimation, and conjunctival absorption.
- To enhance patient comfort, ensure improved compliance, and enhance the therapeutic efficacy of the medication.
- To enhance the housing of the delivery system.
- They can be simply given by the patient alone.

9. Disadvantages of ocular drug delivery systems (37)

- The medication solution remains on the ocular surface for a brief duration.
- It demonstrates inadequate bioavailability.
- Demonstrates the instability of the dissolved medicinal agent.
- Preservatives must be utilized.

10. Classification of ocular medication administration routes (39)

10.1. Invasive drug delivery to intraocular cavities

- Intravitreal surgery (at the pars plana)
- Repeated intravitreal injections
- Intracameral surgery (capsular bag)
- Subretinal injection
- Repeated suprachoroidal injections
- Repeated intracameral injections

10.2. Invasive forms of medication delivery for the periocular and scleral regions

- Intrascleral surgical
- procedure Episcleral surgical procedure
- Repeated periocular injections
- Repeated subconjunctival injections
- Transscleral diffusion from controlled-release systems

10.3. Non-invasive techniques

- Ocular topical administration

10.4. Systemic delivery

- Intravenous administration and injection Orally

11. Ocular gene therapy (40)

Gene therapies in this field have increased significantly over the past few decades, propelled by advancements in viral vector technology and insights into the genetic basis of ophthalmic disorders. This trend resulted in the FDA's approval of Luxturna TM in 2017, the starting medication of its type for treating eye diseases using gene therapy. This significant accomplishment enhances research and clinical focus on gene therapy for a broader range of eye diseases than before. Approximately 350 hereditary ocular disorders exist, including a diverse array of genetic loci, including retinitis pigmentosa, choroideremia, Stargardt disease, and Leber's congenital amaurosis (LCA). Diseases such as retinitis pigmentosa, Stargardt disease, and Leber's congenital amaurosis (LCA) are included. The design of vectors and the encapsulation of transgenes have substantially improved transgene expression and phenotypic recovery after intraocular delivery.

11.1. The conjunctiva

The conjunctiva is located on the ocular surface and the inner surfaces of the eyelids. It consists of several components, all of which, in conjunction with the corneal surface, constitute the conjunctival sac. The visible portion of the sclera is covered by the bulbar conjunctiva.

Table 1 Overview of Routes of Administration, Benefits, and Challenges in Ocular Delivery (41)

Route	**Benefits**	**Challenges**	**Application in the treatment of disease**
Topical	Improved patient compliance, self-administrable and non-invasive	Increases tear dilution and turnover rate, the cornea functions as a barrier, utilizing efflux pumps. BA < 5%	Keratitis, uveitis, conjunctivitis, scleritis, episcleritis, blepharitis
Oral systemic Intravitreal	Patient complaint and non-invasive root of administration Direct administration to the vitreous and retina maintains medication concentrations and bypasses BRB	BAB, BRB heigh dosage causes toxicity BA<2% Retinal detachment, hemorrhage, cataract, endophthalmitis, patient in compliance	Scleritis, episcleritis CMV retinitis, PU AMD, PU AMD, PU, BRVO, CRVO, DME, CME, UME, CMV retinitis
Intracameral	Delivers elevated drug concentrations in the anterior chamber, removes the need for topical drops, and minimizes corneal and systemic adverse effects associated with topical steroid treatment.	TASS, TECDS	Anesthesia, prevention of endophthalmitis, inflammation and pupil dilation
Subconjunctival	Administration to the anterior and posterior segments, location for depot formulations	Conjunctival and choroidal circulation	Glaucoma, CMV retinitis, AMD, PU
Subtenon	Elevated ocular drug concentrations, comparatively noninvasive, and associated with fewer problems than intravitreal administration.	RPE, chemosis, subconjunctival hemorrhage	DME, AMD, RVO, uveitis
Retrobulbar	Administer elevated local dosages of anesthetics, which are more effective than peribulbar techniques, with low impact on intraocular pressure (IOP).	Retrobulbar hemorrhage, globe perforation, respiratory arrest	Anaesthesia
Posterior juxtasclera	Safe for delivery of depot formulations, sustain drug levels up to 6 months to the macula avoid risk of endophthalmitis and intraocular damage	Requires surgery and RPE acts as barrier	AMD

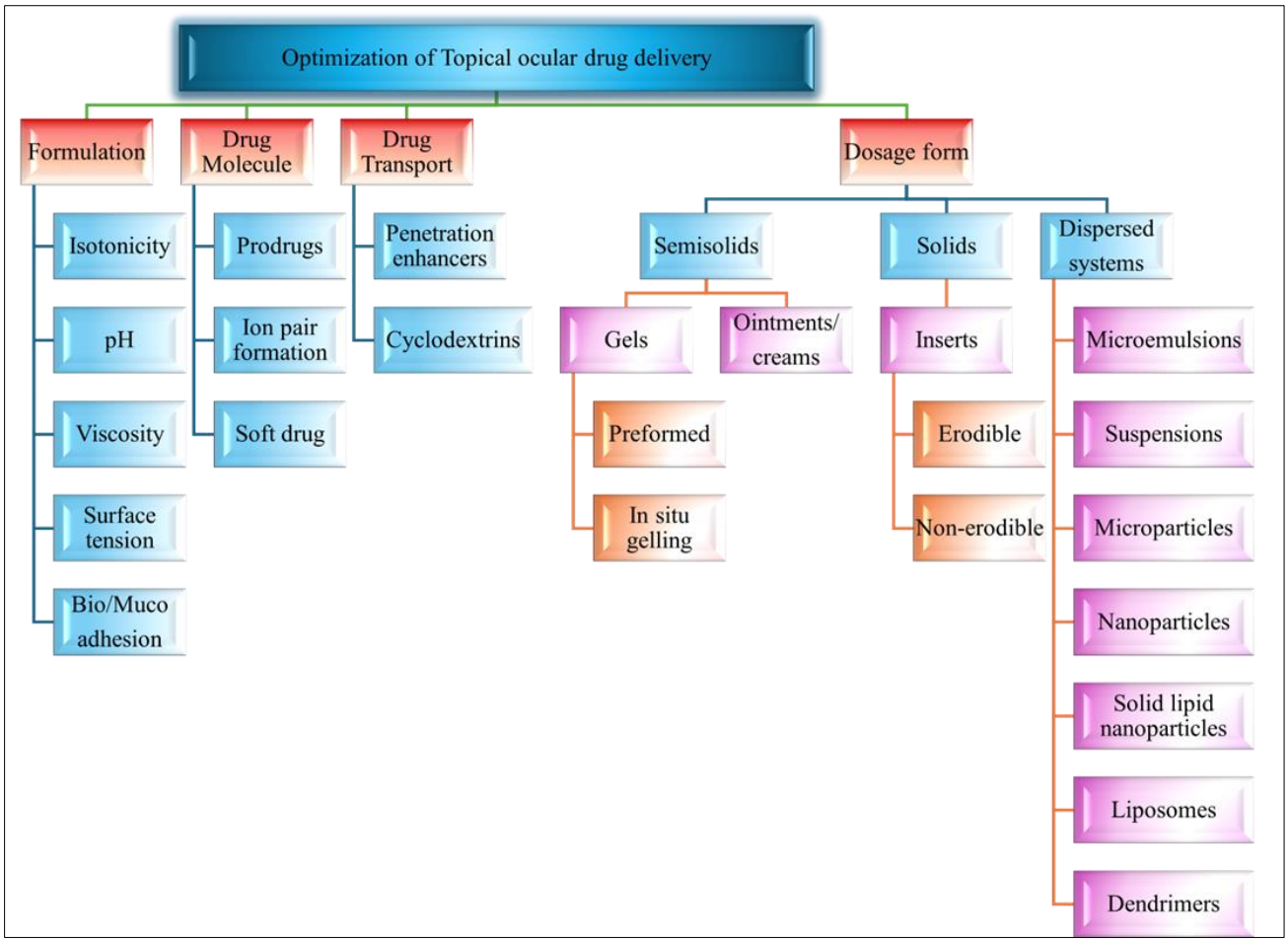

Figure 5 Strategies followed to improve topical ocular drug delivery. (42)

12. Effects of physiological factors on ocular drug delivery approaches (43)

The design and development of medication delivery systems aimed at ocular tissues is a considerable challenge for researchers. The eye is divided into anterior and posterior chambers, and each layer of ocular tissue exhibits anatomical differences that impede drug absorption, irrespective of the route of administration (i.e. topical, systemic, periocular).

Table 2 Comparison of Ocular Drug Delivery Routes: Characteristics, Importance, Drawbacks, and Claims

Route of Administration	Characteristics/Importance	Drawbacks/Limitations	Claims in Ocular Conveyance
Topical	More convenient than non-invasive methods. Easy self-direction.	Nadequate medication permeation and bioavailability. Rapid drug clearance from the ocular surface. Low patient compliance.	Conjunctivitis, dry eye, glaucoma, allergic eye disorders
Subconjunctival Injection	Prolonged drug release. High drug concentrations at the target site.	Invasive administration. Risk of infection and tissue damage	Ocular inflammation, infection, macular edema
Intravitreal Shot	Direct sending to the vitreous. Long duration of drug action.	Risk of endophthalmitis then retinal detachment. Frequent injections are required.	Age-related macular degeneration, diabetic retinopathy

Trans corneal permeation	• Non-invasive and easy administration.	Limited drug permeation across the cornea. Need for penetration enhancers or advanced techniques.	Corneal infections, anterior uveitis
Implantable devices	Sustained drug release. Reduced frequency of administrations.	Invasive implantation procedure. Potential complications associated with the implant.	Glaucoma, retinal diseases
Intracameral	Produces increased medication concentrations in the anterior chamber. Eliminates the necessity for the administration of topical drops. Reduces corneal and subsequently systemic adverse effects associated with the use of topical steroids	Toxic frontal sector ailment. Toxic endothelial cell demolition ailment.	Anesthesia, preclusion of endophthalmitis, irritation and pupil distention.

13. Conclusion

The complex anatomy and physiology of the human eye pose significant challenges to effective ocular drug delivery. This comprehensive review highlights the various ocular drug delivery systems, including topical administration, intravitreal injection, and implantable devices, as well as novel nano-formulations such as nanosuspensions, microemulsions, liposomes, and niosomes. Understanding the advantages and disadvantages of each delivery system is crucial for developing effective treatments for ocular disorders. Ultimately, this study aims to provide a comprehensive overview of ocular drug delivery systems, which will benefit society by improving treatment outcomes for ocular diseases and enhancing patient quality of life.

Compliance with ethical standards

Disclosure of conflict of interest

The authors disclose that no direct or indirect conflicts of interest.

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