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OCULAR DRUG DELIVERY SYSTEMS: A COMPREHENSIVE REVIEW

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ABSTRACT

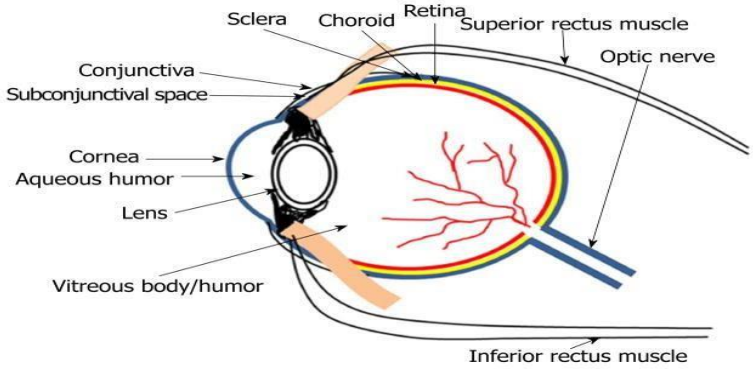
The effective treatment of ocular diseases remains a significant challenge due to the complex anatomy and physiological barriers of the eye, which limit drug penetration and reduce therapeutic efficacy. Conventional ocular drug delivery systems, such as eye drops and ointments, often exhibit poor bioavailability because of rapid tear turnover, nasolacrimal drainage, and limited corneal permeability. Consequently, frequent dosing is required, leading to reduced patient compliance and suboptimal therapeutic outcomes. This review provides a comprehensive overview of ocular drug delivery systems, highlighting both conventional and advanced approaches designed to overcome these limitations. Recent developments, including nanoparticles, liposomes, niosomes, dendrimers, hydrogels, in situ gels, ocular inserts, contact lens-based delivery systems, microneedles, implants, and nanofiber-based carriers, are discussed with respect to their design, mechanism of drug release, advantages, and clinical applications. The review also examines the influence of ocular barriers on drug absorption, strategies for improving ocular bioavailability, and the role of emerging technologies such as stimuli-responsive systems and targeted drug delivery. Furthermore, regulatory considerations, formulation challenges, and future research directions are addressed. Overall, advances in ocular drug delivery technologies have demonstrated significant potential to enhance therapeutic efficacy, prolong drug residence time, minimize systemic side effects, and improve patient adherence. Continued innovation in biomaterials, nanotechnology, and controlled-release systems is expected to facilitate the development of safer, more effective, and patient-friendly ocular therapies for both anterior and posterior segment diseases.

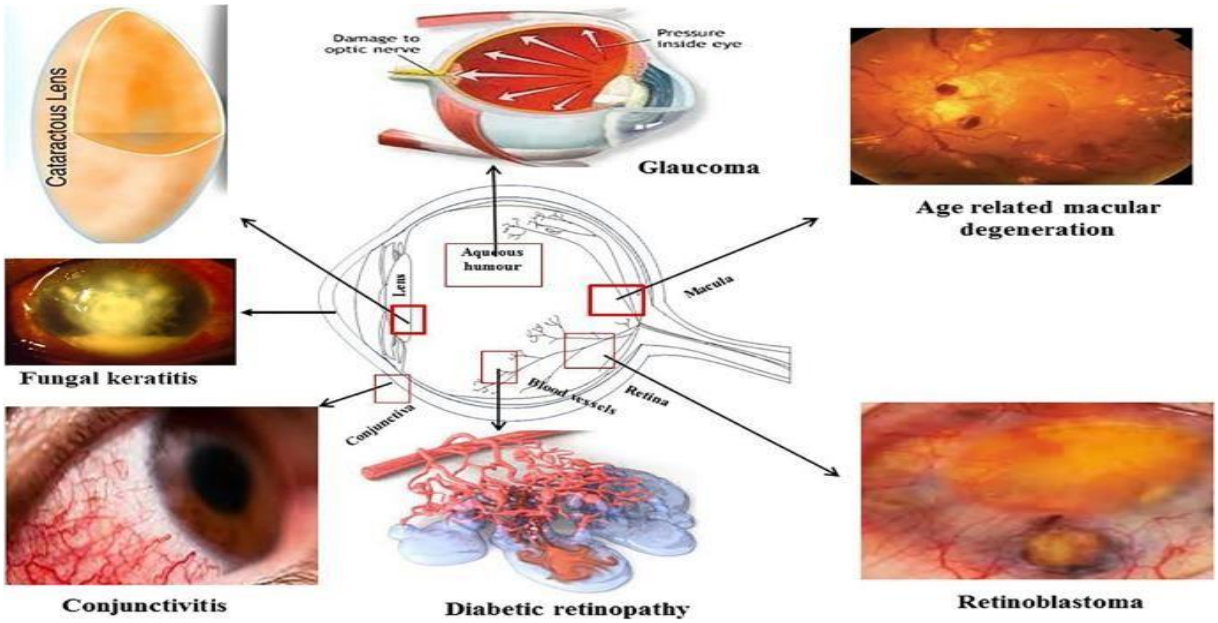
KEYWORDS: Ocular drug delivery, eye diseases, nanoparticles, in situ gel, ocular inserts, liposomes, hydrogels, nanotechnology, controlled drug release, bioavailability.

INTRODUCTION

The eye is a complex organ with a unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye. Eye is a very sensitive organ with a sophisticated physiology. It is composed of anterior and posterior segments. Generally, quality of life is significantly influenced by visual impairment resulted from various diseases. Cataract is the main cause of blindness worldwide. About 40–60% of blindness in the world is caused as a complication of cataract. Early cataract development results from mutations in α, β, and γ crystallin and its associated genes. Although many potent drugs are available to treat most of ocular complaints, there are many ocular barriers such as tear film, corneal, conjunctival, and blood-ocular barriers that hinder their therapeutic efficacy. Conventional eye drops are wasted by blinking and tear flow. Therefore, their bioavailability is minimized to less than 5%.

Structure of the eye





Various Ocular Diseases Affecting the Two Segments of the Eye:

Fungal keratitis

Fungal keratitis or keratomycosis refers to an infective process of the cornea caused by any of the multiple pathologic fungi capable of invading the ocular surface. It is most typically a slow, relentless disease that must be differentiated from other types of corneal conditions with similar presentation; especially its bacterial counterpart, which accounts for the majority of the microbial corneal infections.

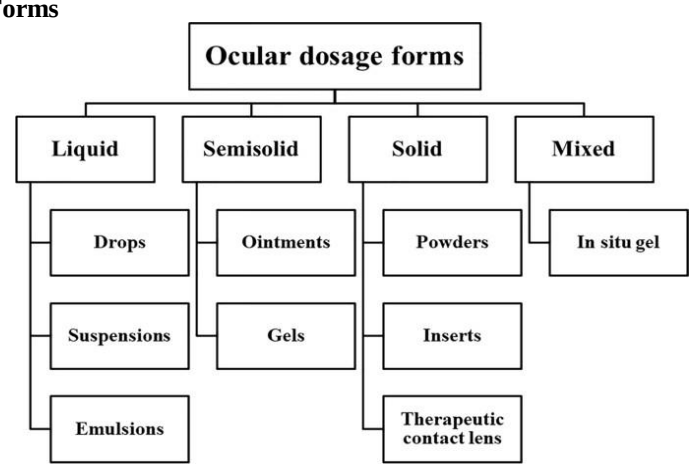
Conjunctivitis

Conjunctivitis, also known as pink eye, is the inflammation of the conjunctiva (thin, translucent tissue lining white parts of the eye) causing the white of the eye to turn pink or red. This is usually due to a viral or bacterial infection, or an allergic condition.

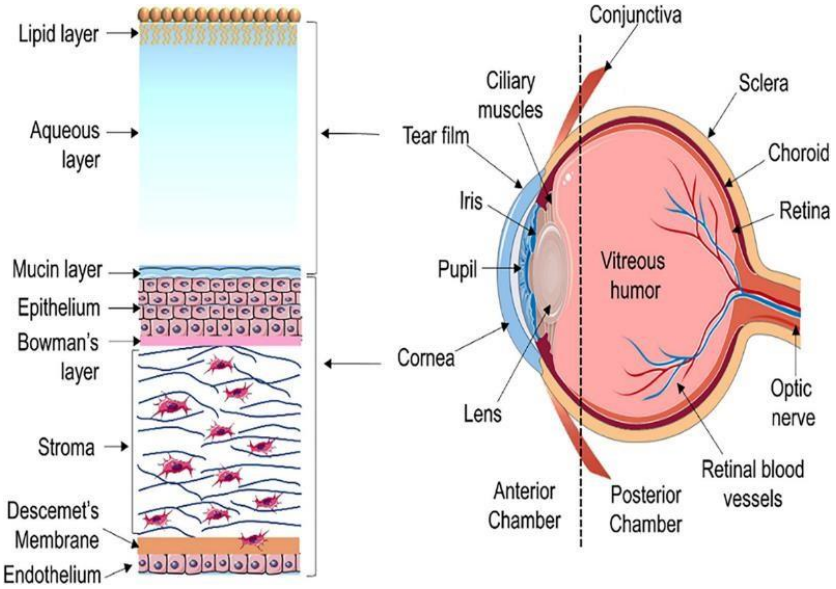
Retinoblastoma

Retinoblastoma is a rare type of eye cancer that can affect young children. It affects the retina, which is at the back of the eye. Retinoblastoma is a rare type of eye cancer that can affect young children. It mostly affects children under 3 years of age. It can be in 1 or both eyes and affects the back of the eye (the retina). The retina sends signals to the brain to help you see. Treatments are available and it can usually be treated successfully if it's found early. Retinoblastoma is often linked to a change in a gene that controls the growth of the eye. It can run in families.

Types of Ocular Dosage Forms



Anatomy of eye



Anterior chamber. The front section of the eye's interior where aqueous humor flows in and out, providing nourishment to the eye.

Aqueous humor. The clear watery fluid in the front of the eyeball.

Blood vessels. Tubes (arteries and veins) that carry blood to and from the eye.

Caruncle. A small, red portion of the corner of the eye that contains modified sebaceous and sweat glands.

Choroid. The thin, blood-rich membrane that lies between the retina and the sclera and is responsible for supplying blood to the outer portion of the retina.

Ciliary body. The part of the eye that produces aqueous humor.

Cornea. The clear, dome-shaped surface that covers the front of the eye.

Iris. The colored part of the eye. The iris is partly responsible for regulating the amount of light permitted to enter the eye.

Lens (also called crystalline lens). The transparent structure inside the eye that focuses light rays onto the retina.

Lower eyelid. Skin that covers the lower part of the eyeball, including the cornea, when closed.

Macula. The central portion of the retina that allows us to see fine details.

Optic nerve. A bundle of nerve fibers that connect the retina with the brain. The optic nerve carries signals of light, dark, and colors to a part of the brain called the visual cortex, which assembles the signals into images and produces vision.

Posterior chamber. The back part of the eye's interior.

Pupil. The opening in the middle of the iris through

which light passes to the back of the eye.

Retina. The light-sensitive nerve layer that lines the inside of the back of the eye. The retina senses light and creates impulses that are sent through the optic nerve to the brain.

Sclera. The white visible portion of the eyeball. The muscles that move the eyeball are attached to the sclera.

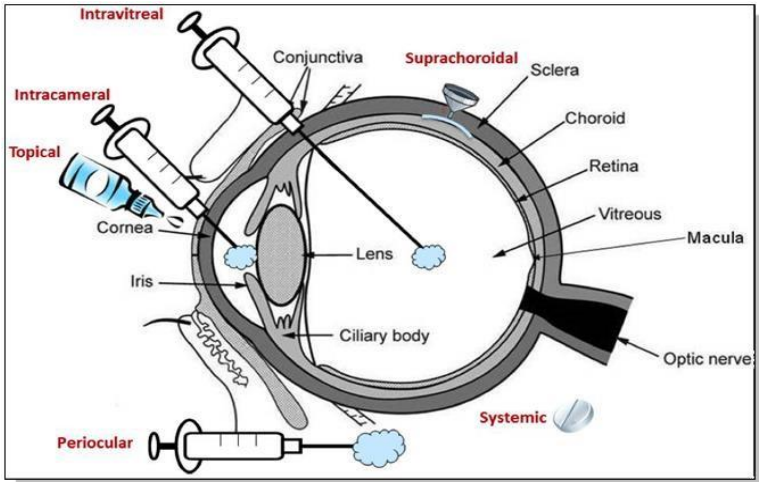
Suspensory ligament of lens. A series of fibers that connects the ciliary body of the eye with the lens, holding it in place.

Upper eyelid. Skin that covers the upper part of the eyeball, including the cornea, when closed.

Vitreous body. A clear, jelly-like substance that fills the back part of the eye.

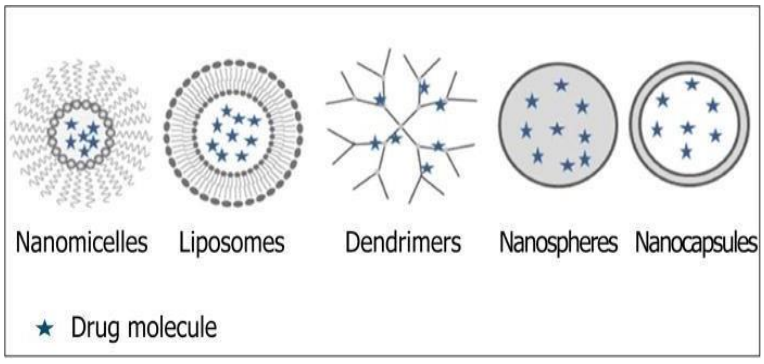
Routes of ocular drug delivery

The various possible routes for ocular drug delivery are described below:



Nanotechnology based ocular drug delivery

In a last few decades, many approaches have been utilized for the treatment of ocular diseases. Nanotechnology based ophthalmic formulations are one of the approaches which is currently being pursued for both anterior, as well as posterior segment drug delivery. Nanotechnology based systems with an appropriate particle size can be designed to ensure low irritation, adequate bioavailability, and ocular tissue compatibility. Several nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nanomicelles and dendrimers have been developed for ocular drug delivery. Some of them have shown promising results for improving ocular bioavailability.



Summary of recent developments with nanoparticles as ocular drug delivery vehicles

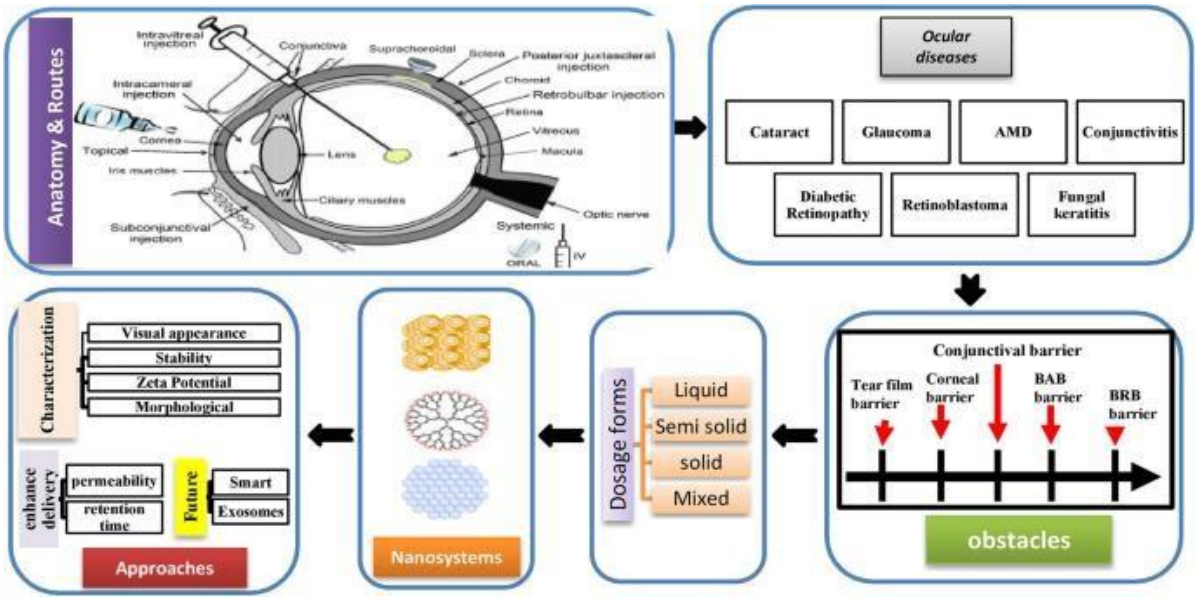
Drug	Polymer	Features
Carboplatin	CH, SA	Carboplatin loaded NPs demonstrated elevated and sustained anti-proliferative activity in a retinoblastoma cell line (Y-79), with IC_{50} of 0.56 and 0.004 µg/mL for free carboplatin and carboplatin loaded NPs, respectively
5-FU	CH, SA	CH coated SA-CH nanoparticles (CH-SA-CH NPs) loaded with 5-FU showed significantly higher concentration of 5-FU in aqueous humor as compared to SA-CH 5-FU loaded NPs and 5-FU solution. The higher C_{max} was achieved in case of CH-SA-CH NPs (24.67 µg/mL) compared to 5-FU solution (6.14 µg/mL)
Sparfloxacin	PLGA	After topical application, sparfloxacin-loaded nanoparticles were retained for a longer duration on the corneal surface as compared to an aqueous solution, which was drained

		rapidly from the corneal surface. Also, *in vitro* release studies revealed an extended release of sparfloxacin
BT	Sodium alginate	BT-loaded nanoparticles provided prolong drug release over a period of 8 h after topical instillation to albino rabbits
Levofloxacin	PLGA	The nanosuspensions was retained for the longer time on rabbit eye surface and drained out slowly compared to marketed formulation. Results of *ex-vivo* transcorneal permeation study across excised goat cornea revealed that levofloxacin from the marketed formulation was permeated 36.9% in 4 h whereas levofloxacin from PLGA nanoparticles was permeated 47.43% in 4 h across cornea
DS	PLGA	An extended DS release was observed from the nanoparticles under *in vitro* conditions. The developed polymer nanoparticles formulation was non-irritant to cornea, iris, and conjunctiva for as long as 24 h after application
Pilocarpine	PLGA	The *in vivo* miosis studies showed that the duration of miotic response increased by 40% for the nanoparticles compared to the eye drops
Brimonidine Tartrate	Eudragit RS 100	The AUC (ΔIOP *vs* time) for the selected nanoparticles formulations

Recent advancements in liposomal ocular drug delivery

Drug	**Type of Liposomes**	**Result**
Acetazolamide	Multilamellar, unilamellar	Multilamellar liposomes produced a more significant lowering in IOP in comparison with REVs liposomes
Ciprofloxacin	Multilamellar	The mean residence time of ciprofloxacin was threefold higher for the CS-coated liposomes (3.85 h) compared to commercially available eye drops Ciprocin® (1.39 h)
VIP	Pegylated liposomes	After intravitreal injection, VIP concentration in ocular fluids was 15 times higher for liposomal formulation (155 ± 65 ng/mL) than the solution (10 ±1 ng/mL), at 24h
Coumarin-6	Multilamellar	After topical administration in mice, the intensity of coumarin-6 in the retina was much higher with PLL modified liposomes
Fluorescence probe (coumarin-6)	Submicron-sized liposomes (ssLips) and multilamellar	After topical instillation of submicron-sized liposomes (ssLips), drug was delivered to the posterior segment ocular tissues including retina
Edaravone	Submicron-sized liposomes	Topical administration of edaravone-loaded ssLips protected retina against light-induced dysfunction in mice eye while there was no marked protection found in the group treated with free edaravone
Diclofenac	Multilamellar	Topical administration of diclofenac loaded PVA-R modified liposomes lead to improved retinal delivery in rabbit eye. Concentration of diclofenac in the retina– choroid was enhanced by 1.8 fold in case of drug loaded PVA-R modified liposome compared to that of the diclofenac solution

REVs: Reverse phase evaporation; PLL: Poly-L-lysine; VIP: Vasoactive intestinal peptide; PVA: Polyvinyl alcohol; IOP: Intraocular pressure; AUC: Area under the curve.



CONCLUSION

The eye is a highly specialized and complex organ protected by multiple anatomical and physiological barriers that significantly limit the effectiveness of conventional drug delivery systems. As a result, achieving adequate drug concentrations at the target site, particularly in the posterior segment, remains a major challenge in the management of ocular diseases. Although traditional formulations such as eye drops and ointments are widely used, their low bioavailability, rapid precorneal elimination, and requirement for frequent administration often lead to poor therapeutic outcomes and reduced patient compliance.

Recent advances in nanotechnology-based ocular drug delivery systems, including nanoparticles, liposomes, niosomes, dendrimers, nanoemulsions, hydrogels, and in situ gel-forming systems, have demonstrated considerable potential to overcome these limitations. These innovative carriers enhance drug stability, improve corneal and conjunctival penetration, prolong ocular residence time, enable controlled and sustained drug release, and reduce systemic exposure and adverse effects. Furthermore, targeted delivery strategies have opened new opportunities for the effective treatment of both anterior and posterior segment disorders, including glaucoma, cataracts, age-related macular degeneration, diabetic retinopathy, and ocular infections.

Despite these encouraging developments, challenges related to long-term safety, large-scale manufacturing, regulatory approval, formulation stability, and cost-effectiveness must be addressed before widespread clinical adoption. Future research should focus on the development of smart, biodegradable, and stimuli-responsive delivery systems with improved targeting efficiency and patient acceptability. Interdisciplinary collaboration among pharmaceutical scientists, clinicians, material scientists, and regulatory agencies will be essential to translate these advanced technologies from laboratory research to clinical practice. Overall, continuous innovation in ocular drug delivery systems holds significant promise for improving therapeutic efficacy, enhancing patient adherence, and ultimately advancing the management of ocular diseases.

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