INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Ocular Drug Delivery System: A Review On Its Recent Advancement

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ARTICLE INFO

Received: 29 Aug 2024
Accepted: 31 Aug 2024
Published: 01 Sep 2024
Keywords:
Ocular, Firms, Advancement, Drug, drops, eyes, Retina
DOI:
10.5281/zenodo.13625775

ABSTRACT

One of the most intriguing and difficult issues facing pharmaceutical firms today is the delivery of drugs to the eyes. The primary issue is the drug's low bioavailability. Compared to traditional dosage forms, controlled drug delivery systems have numerous benefits, such as increased drug bioavailability, decreased toxicity, and reduced frequency of dosing. Ocular medication delivery systems that form in-situ have the potential to address issues such as low bioavailability of ophthalmic solutions due to dilution and ocular drainage. To increase the medications' bioavailability, various dosage forms, including liposomes, microemulsions, and nanoparticles, have been created. Static barriers, which include the various layers of the cornea, sclera, and retina as well as blood-aqueous and blood-retinal barriers, as well as dynamic barriers, which include choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution, can all have an impact on drug delivery. More recent research in ophthalmic drug delivery systems aims to slow down the medication's removal while also prolonging the vehicle's contact duration at the ocular surface. The identification of influx transporters on different ocular tissues and the development of parent drug delivery strategies that target these transporters have gained traction in recent years.

INTRODUCTION

Because of the features of its drug disposition, the eye is the most significant organ. Generally speaking, topical administration is favored over systemic administration. Before a medication molecule may pass through the precorneal barriers and enter the cornea, it must first pass through the anatomical barrier(1). When administered topically, the medicine triggers the physiological defences against ocular drug transport, such as the formation of tears. The nasal cavity's larger surface area and higher permeability of the nasal mucosal membrane allow it to remove medications administered topically from the precorneal area of the nasal mucosal membrane's increased

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

permeability and larger surface area(2). The typical dropper releases 50–75µl of fluid per drop, and some of these drops quickly drain, returning the eye to its typical resident volume of 7µl. Due to drug loss, very little medication is able to reach the cornea and interior tissue of the eye. The drug's actual corneal permeability is relatively low, and in people, the instilled solution typically has a corneal contact time of 1-2 minutes, compared to 10%. In reality, very little of the medication enters the cornea and reaches the intraocular tissue. The majority of ophthalmic medications are applied topically as eye drops, a dosage form made up of the medication suspended in an aqueous solution that has been buffered and isotonic(3). Preparations such as gels, ointments, liposomes, micro and nanoparticles, microspheres, and ocular minitablets (MT) or films can be used to accomplish ophthalmic CDDS. Precorneal medication retention can be increased by adding different polymers of varying grades to viscous gel, colloidal solution, or erodible or non-erodible inserts(4).

PHYSIOLOGY OF EYE:

The vitreous body, lens, and transparent cornea constituents of the eye. The anterior chamber of the eye is filled with 300 µl of aqueous humor in humans. The four structures that make up the lacrimal apparatus are responsible for continuously cleaning and lubricating the eye: lacrimal glands, lacrimal canals, lacrimal sac, nasolacrimal duct. When the eyelids blink, the lacrimal fluid secreted by the lacrimal glands runs over the eyeball and is collected by the eyelids(5). Human lacrimal fluid, an isotonic aqueous solution with a pH of 7.4, has a volume of 7 µl. As seen in the illustration, the anterior and posterior segments of the human eye are separated(6).

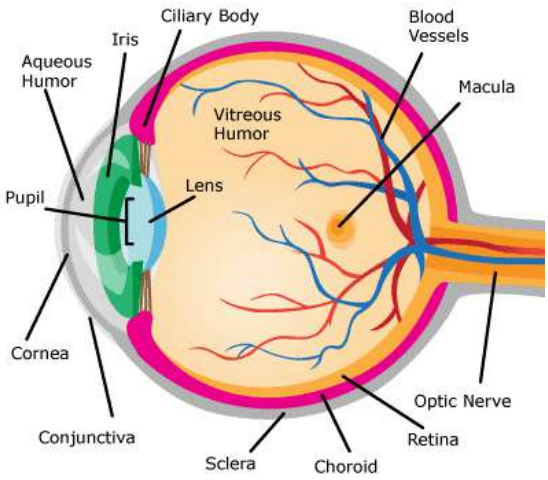

Figure 1 Physiology of Eye

Anterior Segment: The structure of the anterior segment consists of the lens, ciliary body, iris, limbus, anterior and posterior chambers, trabecular meshwork, Schlemm's canal, and zonule.

1. **The cornea:**

It refracts light entering the eye, which then travels through the pupil and onto the lens, serving an essential optical function.

2. **Iris:**

Slender and round, the iris is a contractile curtain situated behind the cornea and in front of the lens. The iris modifies the pupil's size to control the quantity of light that enters the eye.

3. **Pupil:**

being more appropriately defined as the circular aperture in the middle of the iris through which light enters the eye, pupil is commonly perceived as the dark "centre" of the eye.

4. **Lens:**

It is surrounded by the ciliary muscles and situated behind the pupil of the eye. It facilitates the refraction of light entering the eye. Light is focused by the lens onto the retina to create a picture.

5. **Muscle of the Ciliary:**

The central layer of the eye has a ring of smooth, striated muscles called the ciliary muscle. The

lens's curvature is changed by the ciliary muscle's contraction and relaxation.

6. Eyelids:

The conjunctiva secretes significant amounts of fluid, mucins, and electrolytes, which aid in the production of the tear film.

7. Watery humor:

The outer or front chamber of the eye contains a jelly-like material called aqueous humor. Aqueous humor turnover in humans occurs at a rate of between 1% and 1.5% of anterior chamber volume each minute(7, 8).

The Lateral Section:

The vitreous, retina, sclera, choroid, and optic nerves make up the posterior section.

1. Sclera:

The strong white sheath that makes up the ball's outer covering is called the sclera. The tough, fibrous membrane that keeps the eye's roughly globular form in place.

2. The retina:

In the rear of the human eye is where the retina is found. The retina can be thought of as the "screen" onto which light that has entered the eye through the cornea, aqueous humour, pupil, lens, and vitreous humour before reaching the retina forms a picture.

3. Vitreous Humour:

In the human eye, the vitreous humor makes up around 80% of the eye. It is a thin, jelly-like substance that is completely transparent and occupies the space behind the eye's lens.

4. The optic nerve:

The nerve signals that travel from the eye to the brain are carried by the optic nerve. The brain can process the information on an image included in these nerve signals.

5. Macula:

The macula is the name for the retina's central region. Photoreceptor cells, which translate light into nerve signals, are highly concentrated in the macula.

6. Choroid:

It is a very thin, highly vascular membrane with a dark brown color that is pigmented to absorb excess light and keep eyesight from becoming blurry(9, 10).

OBSTACLES TO LIMITING INTRAOCULAR DRUG DELIVERY

1. Tear Film:

One of the precorneal barriers, tear film lowers the effective concentration of the medications administered because of drug molecule binding to the tear proteins and dilution by tear turnover (about 1 μL/min).

2. Cornea

The cornea is made up of three layers: endothelium, stroma, and epithelium. It also has a mechanical barrier that prevents things from leaving the body from entering the eye.

3. The eyelid:

The thin, transparent membrane known as the conjunctiva on the globe and eyelids plays a role in the creation and upkeep of the tear film. The conjunctiva also has an abundant supply of lymphatics and capillaries.

4. Sclera:

Collagen fibers and proteoglycans embedded in an extracellular matrix make up the majority of the sclera.

5. Brucella Membrane/Choroid: One of the body's most vascularized tissues, the choroid supplies blood to the retina. Compared to the brain, it has 10 times more blood flow per unit of tissue weight.

6. The retina:

The posterior route of elimination occurs through retinal permeability. The medications in the subretinal fluid may, in an intact retina, theoretically be absorbed by the sensory retinal blood vessels or carried across the retinal pigment epithelium (RPE) and absorbed into the choroidal vessels or pass through the sclera.

7. The Blood-Retinal Divide:

Medication transport from blood into the retina is limited by the blood-retinal barrier (BRB). BRB is made up of retinal capillary endothelial cells at tight junctions. These endothelial vesicles are thought to be involved in either fluid phase or receptor-mediated endocytosis or transcytosis(1, 11, 12).

OCULAR DRUG DELIVERY SYSTEMS' BENEFITS

1. Simple convenience and needle-free administration of drugs without the requirement for skilled workers.
2. Support for self-medication administration, which 3. improves patient compliance over parenteral methods.
3. The eye can be used to get hydrophilic, low molecular weight medications with good penetration.
4. Due to the huge absorption surface area and quick beginning of action, rapid absorption and
5. Elevated vascularization. Therefore, ocular delivery of a relevant medicine would be a useful alternative to conventional administration routes in emergency treatment.
6. Steer clear of first-pass hepatic metabolism(10, 13-15).

OCULAR DRUG DELIVERY SYSTEMS' DRAWBACKS:

1. The physiological limitation is the cornea's restricted permeability, which results in a poor absorption of eye medications.
2. A significant amount of the dosage that is delivered can have unintended systemic adverse effects since it drains into the lacrimal duct.
3. The medication is rapidly eliminated from the body through tear flow and eye blinking, which shortens the duration of the therapeutic action and necessitates frequent dose schedules(16, 17).

BARRIERS FOR THE OCULAR DELIVERY

1. Drug leakage from the surface of the eyes

Following instillation, the lacrimal fluid flow flushes the injected chemicals off the eye's surface. The systemic absorption of the medicine rather than its ocular absorption is another cause of ineffective drug elimination.

2. Eye and lacrimal fluid barriers

Drug absorption from the lacrimal fluid into the eye is restricted by the corneal epithelium. The formation of tight connections by the corneal epithelial cells restricts the penetration of paracellular drugs. The conjunctiva's surface area is over 20 times larger than the cornea's, and its epithelium is generally more permeable.

3. Blood-ocular barriers

Blood-ocular barriers shield the eye from the xenobiotic in the bloodstream. The endothelial cells in the uvea make up the blood-eye barrier. This barrier restricts the entry of hydrophilic medicines from plasma into the aqueous humor and keeps plasma albumin from entering the aqueous humor(18, 19).

EYE INFECTIONS

Infections of the eyes can be caused by bacteria, fungus, or viruses.

Typical eye diseases include

1. Keratitis/corneal ulcerations

the illness that causes patients to have blurry or foggy corneas, red eyes, impaired vision, and oftentimes eye discomfort.

The primary causes of keratitis include parasites, bacteria, viruses, fungus, and protozoa.

2. The disease of the eyes

It is a severe kind of intraocular inflammation that affects the inner coats of the eyes as well as the ocular cavities. mostly brought on by E. Coli, Pseudomonas, streptococci, etc.

3. The condition of the eyes

The swelling (inflammation) or infection of the conjunctiva, the membrane lining the eyes, is known as conjunctivitis. It is primarily

distinguished by cellular exudation and invasion. Bacterial conjunctivitis is most frequently caused by Staphylococcus aureus.

4. The trachoma

"Active trachoma" refers to the inflammation of the conjunctiva that often affects children, particularly those in preschool. It is distinguished by non-specific inflammation and white masses beneath the upper eyelid's surface. The bacterium Chlamydia trachomatis is the cause of this.

5. Eye Dryness

If the composition of tears is altered, insufficient tear production occurs, leading to dry eyes. In addition to causing ocular pain, dry eye disorders can also cause damage to the cornea(20, 21).

OCCULAR DRUG DELIVERY ROUTES

The three main routes by which ocular drugs are administered to the eye are intravitreal, retrobulbar, and topical local ocular (i.e., subconjunctival).

- **Topical medication:**

The most practical and patient-friendly method of medicine delivery, particularly for treating anterior segment disorders, is topical eye drops. Ocular medication delivery is one of the most difficult and unique methods of administration because of the architecture and physiology of the eye.

- **The subconjunctival pathway:**

Subconjunctival injections bypass the conjunctival epithelial barrier, which limits the pace at which water-soluble medications can permeate the skin. It is a kind of periocular injection method used for ocular drug administration, when a treatment is administered underneath the eyelid's conjunctiva or under the conjunctiva underneath it.

- **Intravital pathway:**

It is a method of administering medication or another chemical that gets the material into the vitreous fluid of the eye. Intravitreal simply means "inside the eye." An intravitreal approach has the benefit of having a therapeutic impact in the targeted retinal tissue right away(22, 23).

HOW DRUGS ARE ABSORBED THROUGH THE EYES?

When drugs are injected into the eye, they must first pass through the cornea before passing via the non-corneal pathways. These non-corneal methods entail drug diffusion via the sclera and conjunctiva.

- **Corneal penetration:**

Drugs enter the cornea through the precorneal gap and pass through the corneal membrane. The majority of eye medications are efficiently absorbed due to the diffusion mechanism across the corneal membrane. The rate and degree at which the transport processes take place determine the effectiveness of the absorption process. The cornea may be thought of as consisting of three basic layers (epithelium, stroma, and endothelium) in terms of transcorneal drug permeability(24, 25).

- **The drainage system of Naso-Lacrimal:**

The secretory system, distributive system, and excretory system are the three components of the nasolacrimal drainage system. The secretory system is made up of reflex secretors, which have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimuli, and fundamental secretors, which are triggered by blinking and temperature changes brought on by evaporating tears. The lachrymal puncta, the superior, inferior, and common canaliculi, the lachrymal sac, and the nasolacrimal duct make up the excretory portion of the nasolacrimal drainage system. Illustrates how the mucosal membrane lining the ducts and lachrymal sac absorbs most of the tears, leaving the nasal channel unabated(26).

OPHTHALMIC PREPARATIONS

1. **Solutions:**

Compared to alternative dosage forms, sterile homogenous solution dosage forms offer several

benefits in terms of formulation and ease of commercial production on a large scale. When creating an aqueous solution, a number of issues need to be taken into account. These include the drug's proper salt selection, solvent solubility, therapeutic systemic impact, ocular toxicity, formulation pKa, and pH influence. The solubility, stability, and corneal permeability of the drugs are among the other stability parameters. These factors are dependent on the formulation's pH, as well as on the ingredients' compatibility, solubility, tonicity, viscosity, and buffering capacity(27).

2.Vacancies

When it comes to complexity and difficulty, ophthalmic suspensions are more demanding than ophthalmic (aqueous) solutions. Numerous issues with the formulation of an ophthalmic solution surfaced, including nonhomogeneity in the dosage form, particle settling, cake formation, and particle aggregation(28).

3. Ointments for eyes.

The semi-solid medicines used for external application are called ointments. Paraffin, a blend of semisolid and solid hydrocarbons with a melting or softening point around body temperature and minimal ocular irritation, is typically used in their formulation. Ointments are helpful in maintaining medication release and increasing drug bioavailability(29).

4. Water-Based Gel

High molecular weight, cross-linked polymers combine to create a three-dimensional network in water to generate aqueous gels, also known as hydrogels. Compared to viscous solutions, gels allow for a longer residence duration in the precorneal region(30).

5. Drops of Eye

Drugs that are ocular or surface-active are frequently delivered as suspensions, emulsions, and solutions. Retention of a solution in the eye can be affected by a number of an eye drop's characteristics, including its viscosity, osmolality, hydrogen ion concentration, and injected volume(31).

6. Gels and Ointments

Ophthalmic ointment vehicles can be used to extend the duration of medication interaction with the external ocular surface and improve drug ocular bioavailability. However, the main negative effects of this dose form, such as matting of the eyelids and blurring of vision, might restrict its use(32).

7. Ophthalmic Inserts:

The goal of ophthalmic inserts is to stay in front of the eye for an extended amount of time. These solid devices are meant to be inserted into the conjunctival sac and slowly release the medication(33).

The following is an explanation of some of the ophthalmic inserts:

Ocular implant that is non-erodible:

The Ocusert and Contact lens are examples of non-erodible ocular implants. Ocusert is a multilayer structure made up of a drug core that is continuously diffused across a layer of copolymer membranes surrounding it on all sides. The sterile preparation known as an ocular insert (Ocusert) extends the drug's residence duration in a controlled release way while minimizing or negating the effects of nasolacrimal damage(34). The medication reservoir in an ocusert is made up of two transparent discs with microporous membrane made of ethylene-vinyl acetate copolymer sandwiched between a thin disc of pilocarpine-alginate complex. The tear fluid can enter the drug reservoir compartment through the microporous membranes, dissolving the medication from the complex, for example Alza-ocusert: Then, for four to seven days, pilocarpine molecules are delivered steadily at a rate of 20 to 40 μg/h. used to treat glaucoma. The solubility of the medication, the thickness of the membrane,

and the makeup of the polymers all affect how quickly drugs diffuse(9, 35).

Ocular erodible implant:

The commercialized erodible medication insert devices are Minidisc, SODI, and Laciserts.

i. **Lacisert: Developed by Merck, Sharp, and Dohme in 1981,**

Lacisert is a sterile rod-shaped device used to treat keratitis sicca and dry eye syndrome. By absorbing water from the cornea and conjunctiva, they work to lubricate the cornea by forming a hydrophilic layer. In the process of making lacrisert, no preservatives are utilized. It has a diameter of 12.7 mm and a length of 3.5 mm. It weighs 5 grams. Keratitis can be effectively treated with lacisert. Within a day, it evaporates(34).

ii. Soluble Ocular Drug, or SODI A little oval wafer called an insert was created for cosmonauts who were unable to utilize eye drops while in weightlessness. It is an oval-shaped, sterile thin film composed of acrylamide, N-vinylpyrrolidone, and ethylacrylate. It is around 15–16 milligrams in weight. It is applied to the treatment of trachoma and glaucoma. It takes ten to fifteen seconds for it to get moist and squishy after being placed into the inferior cul-de-sac. The film distributes the medication for about 24 hours before changing into a viscous polymer mass after 10 to 15 minutes and then polymer solutions after 60 to 90 minutes(36).

Benefits of SODI

1. Daily therapy for trachoma and glaucoma.
2. A single dosage application takes the place of four to twelve eye drops or three to six ointments(37).

c. Minidisc:

In contact with the eye, the minidisc is made up of a contoured disc with a convex front and concave rear surface. With a 4-5 mm diameter, it resembles a little contact lens. The minidisc is composed of butyl-n-poly dimethyl-siloxane, a silicone-based pre-polymer α-ψ-bis (4-methacryloxy). Hydrophilic or hydrophobic minidiscs allow for the extended release of both water-soluble and insoluble medications. It has a 170 hour medication release time(38).

3. Liposomes

Liposomes are naturally occurring lipid vesicles with a diameter of 25–10,000 nm that are biocompatible and biodegradable. They are in close contact with the surfaces of the cornea and conjunctiva, which is advantageous for medications that are poorly absorbed, have a low partition coefficient, or are poorly soluble. This raises the likelihood of ocular drug absorption. Niosomes and Discomes: The primary drawbacks of liposomes are their chemical instability, phospholipid oxidative breakdown, and the expense and impureness of naturally occurring phospholipids. Since niosomes may entrap both hydrophobic and hydrophilic medicines and are more chemically stable than liposomes, they were designed as a means of preventing this. Timolol maleate-loaded discoidal vesicles, or "discomes," based on non-ionic surface-active agents were created and their in vivo characteristics were assessed. Discomes have the potential to be drug delivery vehicles since they release the medication gradually into the ocular region(39).

4. Pharmacosomes

This phrase refers to pure drug vesicles that are produced by amphiphilic pharmaceuticals. When the amphiphilic prodrug is diluted with water, it becomes a pharmacosome. The pharmaceuticals exhibit improved stability on the shelf, easier corneal transit, and a regulated release profile(40).

5. Iontophoresis:

In this process, ions are injected into cells or tissues using a direct current. The important ions for iontophoresis should be the drug's charged compounds. At the anode, positively charged drugs are pushed into the tissues, and vice versa. In addition to being quick, painless, and safe,

ocular iontophoresis administration can also deliver a high concentration of medication to a particular location(41).

6. Dendrimer:

Dendrimers have superior water solubility, bioavailability, and biocompatibility and may be effectively employed for various drug delivery routes. Solutions containing dendrimers with carboxylic and hydroxyl surface groups often have longer residence times(42).

7. Collagen Protector:

Collagen shield was created as a corneal bandage to aid in wound healing. It is essentially made of cross-linked collagen that is constructed from skin tissue from fetal calves. Corneal ulcer healing is aided by the use of an antibiotic topically combined with a shield. Tear fluid softens these devices and forms a thin, malleable film that dissolves over a period of 10, 24, or 72 hours. It is biologically inert, has superior biocompatibility, and stable structure(12).

8. The microemulsion :

Small droplet size (100 nm), improved thermodynamic stability, and a clear appearance are typical characteristics of microemulsions, which are dispersions of water and oil stabilized using surfactant and cosurfactant to minimize interfacial tension. The solubility of the therapeutic molecule, such as indomethacin or chloramphenicol for eye illnesses, is significantly improved by optimizing these components(43).

9. nanoscale fragments:

The water-soluble medications are the primary focus of this strategy. Nanoparticles are particulate drug delivery systems that range in size from 10 to 1000 nm, and they can be used to distribute, encapsulate, or absorb drugs. The primary method used to create nanoparticles for ocular medication administration was emulsion polymerization. Polyalkylcyanoacrylates are the primary materials utilized in the production of ophthalmic nanoparticles. It is possible to add the medications before, during, or after the polymerization(28).

10. Prodrugs:

The best prodrugs for ocular therapy should not only have a high partition coefficient and increased lipophilicity, but also a high degree of enzyme susceptibility, which allows them to be either chemically or enzymatically metabolized to the active parent compound within the cornea or after corneal penetration(29).

11. Enhancers of Penetration:

Enhancing the permeability of corneal epithelial membranes increases drug transport across the cornea. Penetration enhancers can be utilized for this reason. Actin filament inhibitors, chemical substances, bile salts, surfactants, and chelators are a few examples of enhancers(44).

12. Phase Transfer Systems/Insitu Gel System:

The phase transition of a formulation from liquid to gel or solid phase occurs when these systems, absorbed into the cul-de-sac of the eye, increase the viscosity of the medicine in the precorneal region. leading to increased bioavailability due to slower corneal clearance. These systems can be affected by pH, temperature or ion activation(45).

13. Gene therapy:

Along with tissue engineering, gene therapy approaches to treat blindness caused by corneal disease are at the forefront of advanced biomedical research. Corneal diseases are the second leading cause of vision loss after cataracts. Several viruses, including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications(46).

14. Stem cell therapy:

New cell therapies to restore vision are focused on two areas of the eye that are critical for visual function, the cornea and retina. The most successful ocular application has been the use of transplanted limbal stem cells. to regenerate corneal epithelium from a source other than the

patient. Sources of limbal cells include donors, autografts, dead eyes, and (more recently) cells grown in culture. Stem cell therapy has shown great success in certain anterior segment diseases(47).

15. Protein and Peptide Therapy:

The delivery of therapeutic proteins/peptides has received much attention in recent years. One such example is the intravitreal injection of ranibizumab. However; Several limitations such as membrane permeability, large size, metabolism and solubility must be taken into account, limiting their effective delivery. The eye route is not a favourable route for the systemic transport of such large molecules(48).

Table 1 Different Ocular drug delivery system is being studied.

Researcher Name & Year	Title	Drug Name	Dosage Form	Publication
Musarrat Husain Warsi et. al. (2016)	Fabrication and Evaluation of Ketorolac Loaded Cubosome for Ocular Drug Delivery	Ketorolac	Cubosome	Journal of Applied Pharmaceutical Science
Ashish Prakash Gorle et. al. (2009)	Design and Evaluation of Polymeric Ocular Drug Delivery System	Gatifloxacin	Ocuserts	Chemical and Pharmaceutical Bulletin
Kanika Goel (2019)	Formulation Development of Natamycin Loaded Nanoemulsion for Ocular Drug Delivery	Natamycin	Nanoemulsion	Science Citation Index Expanded
Guzel K. Abilova et. al. (2019)	Chitosan/poly(2-ethyl-2-oxazoline) films for ocular drug delivery: Formulation, miscibility, in vitro and in vivo studies	Chitosan/poly(2-ethyl-2-oxazoline)	Films	Brazilian Journal of Pharmaceutical Sciences
Soumya Narayana et. al. (2022)	Design and evaluation of ocular hydrogel containing combination of ofloxacin and dexamethasone for the treatment of conjunctivitis	Ofloxacin and dexamethasone	Ocular hydrogel	Brazilian Journal of Pharmaceutical Sciences
Shiva Taghe et. al. (2019)	Preparation and characterization of novel, mucoadhesive ofloxacin nanoparticles for ocular drug delivery	Ofloxacin	Nanoparticles	Brazilian Journal of Pharmaceutical Sciences
Srashti Katiyar et. al. (2022)	Formulation and characterization of eudragit RS 100 nanosuspension for ocular delivery of Indomethacin	Indomethacin	Nanosuspension	INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT

Devu.Satya Sireesha et. al. (2022)	Formulation and evaluation of ocular inserts of diclofenac sodium for controlled release drug delivery	Diclofenac	Ocular inserts	INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT
Sefa Gözcü et. al. (2024)	Formulation of hesperidin-loaded in situ gel for ocular drug delivery: a comprehensive study	Hesperidin	In situ gel	Science Citation Index Expanded
Shahla Mirzaeei et. al. (2017)	Design and Evaluation of Soluble Ocular Insert For Controlled Release of Chloramphenicol	Chloramphenicol	Ocular Insert	Journal of Reports in Pharmaceutical Sciences
Fulchan ALI et. al. (2022)	Formulation and evaluation of acetazolamide loaded in–situ gel for the treatment of glaucoma	Acetazolamide	In–situ gel	Journal of Research in Pharmacy
Neslihan ÜSTÜNDAĞ OKUR et. al. (2023)	In situ gels loaded with naringin as ocular drug delivery carriers; development and preliminary characterization	Naringin	In–situ gel	Journal of Research in Pharmacy
Tasneem Ara et. al. (2014)	Preparation and evaluation of ocular inserts of diclofenac sodium for controlled drug delivery	Diclofenac sodium	Ocular inserts	Scholars Research Library
Esther Prieto et. al. (2020)	Dexamethasone delivery to the ocular posterior segment by sustained-release Laponite formulation	Laponite	Ocular posterior segment	Biomedical Materials
AAYUSH KUMAR JHA et. al. (2019)	Vesicular carrier loaded in-situ thixotropic formulations for Glaucoma: an overview of recent advancement in ocular drug delivery System	Acetazolamide, Timolol maleate, Latanoprost	Loaded in-situ thixotropic formulations	Mintage Journal of Pharmaceutical & Medical Sciences
Grace Rathnam et. al. (2024)	Formulation and evaluation of Dorzolamide hydrochloride microsponges loaded in	Dorzolamide hydrochloride	Microsponges loaded in situ gel	World Journal of Biology Pharmacy and Health Sciences

	situ gel for ocular administration			
Ch. Pujitha et. al. (2017)	Formulation and characterization of ofloxacin opthalmic gel	Ofloxacin	Opthalmic gel	Indian Journal of Pharmacy and Pharmacology
Anroop B. Nair et. al. (2020)	Experimental design, formulation and in vivo evaluation of a novel topical in situ gel system to treat ocular infections	Moxifloxacin	Novel topical in situ gel	PLOS ONE
Esther Prieto et. al. (2020)	Dexamethasone delivery to the ocular posterior segment by sustained-release Laponite formulation	Dexamethasone	Ocular posterior segment	IOP Publishing
Grace Rathnam et. al. (2024)	Formulation and evaluation of Dorzolamide hydrochloride microsponges loaded in situ gel for ocular administration	Dorzolamide hydrochloride	Microsponges loaded in situ gel	World Journal of Biology Pharmacy and Health Sciences

PHARMACEUTICAL REQUIREMENTS (49-53)

1. **Tonicity and tonic-regulating agents:**

tear fluid is isotonic with blood and its isotonic value corresponds to that of 0.9% sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value. Common tonicity regulating ingredients are NaCl, KCl, buffer salts, dextrose.

2. **pH control and buffers:**

The pH and buffering of the ophthalmic solution are probably equally important for proper storage. In addition to stability effects, pH regulation can affect convenience, safety and product activity. Ideally, each product is buffered to a pH of 7.4, which is considered the normal physiological pH of tear fluid.

3. **Stabilizers:**

Stabilizers are ingredients that are added to a formulation to reduce the rate of degradation of the active ingredients. Antioxidants are the main stabilizers added to some ophthalmic solutions, mainly epinephrine and other oxygenating drugs. Ascorbic acid and acetylcysteine, sodium bisulfite, 8-hydroxyquinolone and isoascorbic acid are other commonly used antioxidants.

4. **Surfactants:**

the use of surfactants in the preparation of eye solutions is severely limited. Many nonionic surfactants are used in relatively low concentrations. Mainly used are sorbitan ethers of oleic acid (polysorbate or Tween 20 and 80) and polyoxyl-40-stearate.

5. **Tissue thickening agents:**

polyvinyl alcohol, methyl cellulose, HPMC, hydroxyethyl cellulose and carbomer are used to increase the viscosity of ophthalmic solutions and prevent them. Although the surface area is very small, its main advantage is to increase the eye contact time, which reduces the shrinkage rate and increases the bioavailability of the drug.

6. **Excipient:**

The eye drops are liquid, but only slightly, and use USP purified water as a solvent. All eye drops must be pure. When oils are used as vehicles for ophthalmic fluids, they must be very pure. Vegetable oils such as olive oil, castor oil and sesame oil were used in improvised combinations.

Table 2 Ocular Drug Delivery systems formulation Patents

Sr. No	Patent name and Patent year	Application	Name of Patent Inventor/s
1	Stable Liposomal formulations for Ocular Drug Delivery (2018)	US9956195B2	Subramanian Venkatraman, Jayaganesh V. Natarajan, Tina Howden, Freddy Boey
2	Liposomal formulation for ocular drug delivery (2019)	US10272040B2	Subramanian Venkatraman, Jayaganesh V. Natarajan, Tina Wong, Tin Chiang Freddy Boey
3	Subconjunctival depot forming formulation for ocular drug delivery (2017)	US20190133931 A1	Subramanian Venkatraman, Rini Rachel Joseph, Yin Chiang Freddy Boey
4	Glycosaminoglycan-coated metallic nanoparticles and uses therefor (2024)	US20180049992 A1	Nigel James Fullwood
5	Topical drug delivery systems for ophthalmic use (2010)	WO2010144194	Ashim K. Mitra, Poonam R. Velagaleti, Ulrich M. Grau
6	Omega-3 oils containing ophthalmic emulsions (2010)	WO2010141591	Zhi-Jian Yu
7	Controlled release dispensing device (2010)	WO2010123563	Libin Barry, Jefferey M. Liebmann, Weilliam Chen
8	Ophthalmic drug delivery systems (2009)	EP1534202	Anuj Chauhan, Derya Gulsen
9	Hypercompressed particles for controlled release of ophthalmic medications (2008)	WO2008143906	Barry Libin, Jeffrey M. Liebmann, Weilliam Chen
10	Ophthalmic Nanoparticulate Formulation of a Cyclooxygenase-2-Selective Inhibitors (2008)	US2008/0145430 A1	Santipharp Panmai, Laman L. Alani

11	Cyclodextrine nanotechnology for ophthalmic drug delivery (2007)	WO2007012974	Thorsteinn Loftsson, Einar Stefansson
12	Hydrogel nanocomposites for ophthalmic applications (2007)	US2007/0269488 AI	Nathan Ravi
13	Method for the production of nanoparticles and microparticles (2006)	WO2006137856	Adrian T. Raiche, Joseph C. Salamone
14	Non-invasive ocular drug delivery (2004)	US20040071761	David Miller, S. Li, William Higuchi
15	Ophthalmic Drug Delivery devices (2004)	US20040096477	Anuj Chauhan, Derya Gulsen
16	Ophthalmic Drug Delivery devices (2004)	US20040241207	Anuj Chauhan, Derya Gulsen
17	Nanoemulsion Based on Ethylene Oxide and Propylene Oxide Block Copolymers (2002)	US6464990B2	Jean-Thierry Simonnet, Odile Sonneville, Sylvie Legret
18	Submicrone Emulsions as ocular drug delivery vehicles (2000)	EP0656779	Haim Aviv, Doron Friedman, Amir Bar-Ilan, Micha Vered

EVALUATION OF OCULAR DRUG DELIVERY SYSTEMS (54-60)

In Vitro Evaluation Methods: Different operators use different methods to perform in vitro evaluation of surface drug delivery systems. These include the bottle method, roller/paddle basket method, and flow through device.

1. **Bottle Method:**

In this method, the culture is placed in a culture bottle containing a phosphate buffer solution at pH 7.4. Shake the culture flask in a water bath heated to 37 °C. Media are sampled at appropriate intervals and analyzed for drug content.

2. **Distribution Method:**

In this method, a suitable simulation tool is used. The drug solution is placed in the release compartment and the buffer solution in the acceptor compartment. Artificial gravel or goat cheese is placed between the donor and recipient sections. Diffusion of drugs in the adjuvant phase is measured at different times.

3. **Modified Rotating Basket Method:**

In this method, the structure is placed on a set of baskets connected to the transformer. Pour the mixture into a lined beaker fitted with a sterile plate. The system temperature is maintained at 37 °C. Media are sampled at appropriate intervals and analysed for drug content.

4. **Modified Rotary Vane Apparatus:**

In this method, diffusion cells (cells used for solid state formation analysis) are placed in a container in a rotating vane apparatus. Add the preservative medium to the flask and spin the paddle at 50 rpm. The entire device is maintained at 37±0.5 °C. Whenever necessary, parts of the sample are taken and analysed to determine the drug content.

5. Flow device:

A continuous fluid circulation device is used as the flow device. The device consists of a glass melting cell, a continuously working vibrating pump, a water bath and a spring. The dosage form is then placed in a solvent reservoir. The whole assembly was kept at a temperature of 37 °C. The production volume is distributed throughout the device. A sample of the matrix is taken at different times and analysed for drug content.

6. In vivo evaluation methods:

Rabbits are used as experimental animals due to their facial and body morphology. Drug concentrations in various ocular tissues (eg, lens, cornea, iris, ciliary body, retinal sclera, aqueous humor, and vitreous) are measured for pharmacokinetic studies in rabbits. Intraocular pressure is measured with a tonometer. Ocular pharmacokinetic studies can also be performed using tear collection, a non-invasive method. To drain the aqueous humor, the rabbit was injected with ketamine and approximately 2 ml of the aqueous humor was drained from the anterior chamber.

SUMMARY

Ophthalmic drug delivery systems allow local and systemic delivery of drugs. The latest available targeted drug delivery systems focus on the local delivery of drugs as well as certain macromolecular substances such as proteins, genes such as DNA, siRNA to the inner parts of the eye. Ophthalmic drug delivery system is a field where most researchers are taking challenges to fight various problems related to its delivery. The primary requirement for a successful controlled release product focuses on increasing patient acceptance of Insitu gels. The use of polymeric In-situ gels for controlled release of various drugs offers several advantages compared to conventional dosage forms. These types of formulations are now used daily to treat glaucoma, dry eye, Sjogren's syndrome, and trachoma. Currently, very few new ophthalmic drug delivery systems have been introduced to the market, where they have mostly been used as ocular spacers. Patient acceptance is very important in the design of any convenient ophthalmic drug delivery system. Major improvements are needed in each system, such as improved sustained drug release, large-scale production, and stability. In the future, an ideal system should be able to achieve effective drug concentration in the target tissue for long periods of time while minimizing systemic exposure, and the system should be both convenient and easy to use.

REFERENCE:

1. Mandal S, Shiva K, Kumar KP, Goel S, Patel RK, Sharma S, et al. Ocular drug delivery system (ODDS): Exploration the challenges and approaches to improve ODDS. Journal of Pharmaceutical and Biological Sciences. 2021;9(2):88-94.
2. Gupta B, Mishra V, Gharat S, Momin M, Omri A. Cellulosic polymers for enhancing drug bioavailability in ocular drug delivery systems. Pharmaceuticals. 2021;14(11):1201.
3. Rozi MF, Sabere ASM. A review on conventional and novel topical ocular drug delivery system. Journal of Pharmacy. 2021;1(1):19-26.
4. Nayak K, Choudhari MV, Bagul S, Chavan TA, Misra M. Ocular drug delivery systems. Drug Delivery Devices and Therapeutic Systems: Elsevier; 2021. p. 515-66.
5. Yang Y, Lockwood A. Topical ocular drug delivery systems: Innovations for an unmet need. Experimental Eye Research. 2022;218:109006.
6. Ahmed S, Amin MM, Sayed S. Ocular drug delivery: a comprehensive review. AAPS PharmSciTech. 2023;24(2):66.
7. Grassiri B, Zambito Y, Bernkop-Schnürch A. Strategies to prolong the residence time of drug delivery systems on ocular surface.

Advances in colloid and interface science. 2021;288:102342.
8. Dosmar E, Walsh J, Doyel M, Bussett K, Oladipupo A, Amer S, et al. Targeting ocular drug delivery: an examination of local anatomy and current approaches. Bioengineering. 2022;9(1):41.
9. Tian B, Bilsbury E, Doherty S, Teebagy S, Wood E, Su W, et al. Ocular drug delivery: advancements and innovations. Pharmaceutics. 2022;14(9):1931.
10. Liu L-C, Chen Y-H, Lu D-W. Overview of recent advances in nano-based ocular drug delivery. International Journal of Molecular Sciences. 2023;24(20):15352.
11. Kang-Mieler JJ, Rudeen KM, Liu W, Mieler WF. Advances in ocular drug delivery systems. Eye. 2020;34(8):1371-9.
12. Bisen AC, Biswas A, Dubey A, Sanap SN, Agrawal S, Yadav KS, et al. A review on polymers in ocular drug delivery systems. MedComm–Biomaterials and Applications. 2024;3(2):e77.
13. Mostafa M, Al Fatease A, Alany RG, Abdelkader H. Recent advances of ocular drug delivery systems: prominence of ocular implants for chronic eye diseases. Pharmaceutics. 2023;15(6):1746.
14. Mittal C, Amle VS, Kumar R, Sood P, Uniyal A, Singh H. Recent Advancement in Ocular Drug Delivery System: A Systematic Review. Journal for Research in Applied Sciences and Biotechnology. 2023;2(3):238-49.
15. Shafiq M, Rafique M, Cui Y, Pan L, Do C-W, Ho EA. An insight on ophthalmic drug delivery systems: focus on polymeric biomaterials-based carriers. Journal of Controlled Release. 2023;362:446-67.
16. Batur E, Özdemir S, Durgun ME, Özsoy Y. Vesicular Drug Delivery Systems: Promising Approaches in Ocular Drug Delivery. Pharmaceuticals. 2024;17(4):511.
17. Almeida H, Silva AC. Nanoparticles in Ocular Drug Delivery Systems. MDPI; 2023. p. 1675.
18. Glover K, Mishra D, Gade S, Lalitkumar K, Wu Y, Paredes AJ, et al. Microneedles for advanced ocular drug delivery. Advanced Drug Delivery Reviews. 2023:115082.
19. Xie G, Lin S, Wu F, Liu J. Nanomaterial-based ophthalmic drug delivery. Advanced drug delivery reviews. 2023:115004.
20. Abdelmohsen HA, Copeland NA, Hardy JG. Light-responsive biomaterials for ocular drug delivery. Drug Delivery and Translational Research. 2023;13(8):2159-82.
21. Chakraborty M, Banerjee D, Mukherjee S, Karati D. Exploring the advancement of polymer-based nano-formulations for ocular drug delivery systems: An explicative review. Polymer Bulletin. 2023;80(11):11759-77.
22. Billowria K, Sandhu NK, Singh B. Topical advances in mucoadhesive ocular drug delivery system. Current Drug Delivery. 2023;20(8):1127-40.
23. Qi Q, Wei Y, Zhang X, Guan J, Mao S. Challenges and strategies for ocular posterior diseases therapy via non-invasive advanced drug delivery. Journal of Controlled Release. 2023;361:191-211.
24. Gabai A, Zeppieri M, Finocchio L, Salati C. Innovative strategies for drug delivery to the ocular posterior segment. Pharmaceutics. 2023;15(7):1862.
25. Agarwal P, Rupenthal ID. Non-aqueous formulations in topical ocular drug delivery–A paradigm shift? Advanced Drug Delivery Reviews. 2023;198:114867.
26. Binkhathlan Z, Ali R, Alomrani AH, Abul Kalam M, Alshamsan A, Lavasanifar A. Role of polymeric micelles in Ocular Drug Delivery: an overview of decades of Research. Molecular Pharmaceutics. 2023;20(11):5359-82.

27. Awwad S, Ibeanu N, Liu T, Velentza-Almpani A, Chouhan N, Vlatakis S, et al. Real-Time Monitoring Platform for Ocular Drug Delivery. Pharmaceutics. 2023;15(5):1444.
28. Mishra A, Shaima K, Sindhu RK. Novel Drug Delivery System for Ocular Target. Nanotechnology and Drug Delivery. 2024:205-49.
29. Weber C, Quintin P, Holz FG, Fea A, Mercieca K. Ocular drug delivery systems: glaucoma patient perceptions from a German university hospital eye clinic. Graefe's Archive for Clinical and Experimental Ophthalmology. 2024;262(2):545-56.
30. Virmani T, Kumar G, Sharma A, Pathak K. An overview of ocular drug delivery systems—conventional and novel drug delivery systems. Nanotechnology in Ophthalmology. 2023:23-48.
31. Kaur S, Sohnen P, Swamynathan S, Du Y, Espana EM, Swamynathan SK. Molecular nature of ocular surface barrier function, diseases that affect it, and its relevance for ocular drug delivery. The Ocular Surface. 2023;30:3-13.
32. Lu P, Liang Z, Zhang Z, Yang J, Song F, Zhou T, et al. Novel nanomicelle butenafine formulation for ocular drug delivery against fungal keratitis: In Vitro and In Vivo study. European Journal of Pharmaceutical Sciences. 2024;192:106629.
33. Kandpal N, Nainwal N, Ale Y, Semwal Y, Jakhmola V, Padiyar N. Proniosomes: a pro vesicular system in ocular drug delivery. J Adv Biotechnol Exp Ther. 2023;6(3):622-37.
34. Allyn MM, Luo RH, Hellwarth EB, Swindle-Reilly KE. Considerations for polymers used in ocular drug delivery. Frontiers in Medicine. 2022;8:787644.
35. Chandra NS, Gorantla S, Priya S, Singhvi G. Insight on updates in polysaccharides for ocular drug delivery. Carbohydrate Polymers. 2022;297:120014.
36. Sakpal D, Gharat S, Momin M. Recent advancements in polymeric nanofibers for ophthalmic drug delivery and ophthalmic tissue engineering. Biomaterials Advances. 2022;141:213124.
37. Jiménez-Gómez Y, Alba-Molina D, Blanco-Blanco M, Pérez-Fajardo L, Reyes-Ortega F, Ortega-Llamas L, et al. Novel treatments for age-related macular degeneration: a review of clinical advances in sustained drug delivery systems. Pharmaceutics. 2022;14(7):1473.
38. Sharma DS, Gulati M, Singh SK, Singh PK, Wadhwa S. Role of novel drug delivery systems in overcoming the challenges associated with intraocular delivery of drugs: an overview. Multifunctional Nanocarriers. 2022:401-18.
39. Polat HK, Kurt N, Aytekin E, Bozdağ Pehlivan S, Çalış S. Novel drug delivery systems to improve the treatment of keratitis. Journal of ocular pharmacology and therapeutics. 2022;38(6):376-95.
40. Tatykhanova GS, Aseyev V, Vamvakaki M, Khutoryanskiy VV, Kudaibergenov SE. Ophthalmic drug delivery system based on the complex of gellan and ofloxacin. Chemical Bulletin of Kazakh National University. 2022;2:4-12.
41. Qamar Z, Qizilbash FF, Iqubal MK, Ali A, Narang JK, Ali J, et al. Nano-based drug delivery system: recent strategies for the treatment of ocular disease and future perspective. Recent Patents on Drug Delivery & Formulation. 2019;13(4):246-54.
42. Bachu RD, Chowdhury P, Al-Saedi ZH, Karla PK, Boddu SH. Ocular drug delivery barriers—role of nanocarriers in the treatment of anterior segment ocular diseases. Pharmaceutics. 2018;10(1):28.

43. Bisen AC, Srivastava S, Mishra A, Sanap SN, Biswas A, Choudhury AD, et al. Pharmaceutical Emulsions: A Viable Approach for Ocular Drug Delivery. Journal of Ocular Pharmacology and Therapeutics. 2024;40(5):261-80.
44. Sahoo SK, Dilnawaz F, Krishnakumar S. Nanotechnology in ocular drug delivery. Drug discovery today. 2008;13(3-4):144-51.
45. Mudgil M, Gupta N, Nagpal M, Pawar P. Nanotechnology: a new approach for ocular drug delivery system. Int J Pharm Pharm Sci. 2012;4(2):105-12.
46. Weng Y, Liu J, Jin S, Guo W, Liang X, Hu Z. Nanotechnology-based strategies for treatment of ocular disease. Acta pharmaceutica sinica B. 2017;7(3):281-91.
47. Jóhannesson G, Stefánsson E, Loftsson T. Microspheres and nanotechnology for drug delivery. Retinal Pharmacotherapeutics. 2016;55:93-103.
48. Gade S, Glover K, Mishra D, Sharma S, Guy O, Donnelly RF, et al. Hollow microneedles for ocular drug delivery. Journal of Controlled Release. 2024;371:43-66.
49. PawarC PK, RathodB RD, JagadaleB SR. A review on topical ophthalmic drug delivery system: Reference to viscosity enhancer. Polim Med. 2024;54(1):71-84.
50. Ramos MF, Attar M, Seals JR, Luhrs KA. Safety evaluation of ocular drugs. A comprehensive guide to toxicology in nonclinical drug development. 2024:879-944.
51. Khan J, Khan A, Khan A, Khan D, Shaikh AH, Baig MS. In situ Gel: A Promising Ocular Drug Delivery System. International Journal of Advancement in Life Sciences Research. 2024;7(3):65-77.
52. Singh S, Devi A, Sharma S, Sabharwal S, Sharma S, Dhiman S, et al. A Review on Microspheres and Its Role in Different Drug Delivery System as a Novel Approach. International Journal of Pharmaceutical Sciences. 2024;2(6):1112-26.
53. Pardeshi S, Pillai D, Giram P, Pardeshi C, Gholap A, Naik J. Nanocarriers for ocular drug delivery. Nanocarrier Drug Delivery Systems: Therapeutic and Diagnostic Medicine. 2024:469.
54. Ruan M, Wang R, He Y. Novel Drug Delivery Systems for the Management of Fungal Keratitis. Journal of Ocular Pharmacology and Therapeutics. 2024;40(3):160-72.
55. Tashima T. Ocular Drug Delivery into the Eyes Using Drug-Releasing Soft Contact Lens. Future Pharmacology. 2024;4(2):336-51.
56. Shajari G, Erfan-Niya H, Fathi M, Amiryaghoubi N. In situ forming hydrogels based on modified gellan gum/chitosan for ocular drug delivery of timolol maleate. International Journal of Biological Macromolecules. 2024:135071.
57. Liu B, Chen K. Advances in Hydrogel-Based Drug Delivery Systems. Gels. 2024;10(4):262.
58. da Silva Gonçalves M, Cabral LM, de Sousa VP, do Carmo FA. Development of Ocular Delivery Systems for Macitentan and Ex Vivo Study of Intraocular Permeation. Journal of Drug Delivery Science and Technology. 2024:106023.
59. Pillai AR, Prajapati B, Dharamsi A. Protein Nanoparticles Laden In situ Gel for Topical Ocular Drug Delivery. Current Drug Delivery. 2024;21(1):38-51.
60. Bokatyi AN, Dubashynskaya NV, Skorik YA. Chemical modification of hyaluronic acid as a strategy for the development of advanced drug delivery systems. Carbohydrate Polymers. 2024:122145.

HOW TO CITE: Prajapati Rahul Vinitbhai , Chainesh N. Shah , Umesh Upadhyay , Ocular Drug Delivery System: A Review On Its Recent Advancement , Int. J. of Pharm. Sci., 2024, Vol 2, Issue 9, 79-96. https://doi.org/10.5281/zenodo.13625775