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Review Article

Eye Drops to smart gels: The future of ocular drug delivery

Rajveer Bhaskar, Monika Ola, Vaishnavi Madwe *, Rohini Tikhe, Arun Pawar, Shivani Khade, Sunil Shinde

Department of Pharmaceutics, R. C. Patel Institute of Pharmacy, Shirpur, Dhule, Maharashtra, India 425405

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*Address for Correspondence:

Vaishnavi Devidas Madwe, Department of Pharmaceutics, R. C. Patel Institute of Pharmacy, Shirpur, Dist. Dhule 425405, Maharashtra, India.

Abstract

This review paper assesses traditional and modern methods to enhance ocular drug delivery. Various techniques available to administer drugs include topical application, intracameral injections, intravitreal injections, and subconjunctival injections. In Addition, this review discusses eye anatomy and the associated challenges with effectively delivering medications to this organ. It emphasizes recent progress in Ophthalmic drug delivery methods, such as on-situ gel systems, nanoparticles, liposomes, and dendrimers, which improve drug retention, bioavailability, and therapeutic efficacy. The article also explores potential improvements in drug delivery for treating eye disorders by utilizing nanotechnology and stimulus-responsive gels to improve patient outcomes. The goal is to achieve targeted and continuous release.

Keywords: Ocular drug delivery, in-situ gel, nano formulation, prolonged release.

A. Introduction

The ocular drug delivery system (ODDS) seems to be both necessary and difficult. The eye is the most delicate organ of the body. Furthermore, because of the quick and thorough removal of medications from the pre-corneal lachrymal fluid by solution drainage, lachrymation, and ineffective absorption by the conjunctiva, traditional ophthalmic formulations have a short pre-corneal residence period and poor bioavailability [1]. Most recent studies (ODDS) focus on integrating multiple drug delivery methods, like a build-up system which prolongs the vehicle's contact time on the ocular surface and delays excretion [2, 3]. The In-situ gelling system is initially a liquid that is converted into a gel after being instilled into the eye. By exposing it to the ocular environment. This prolongs precorneal residence time and improves ocular bioavailability. The In-situ gelling system depends upon various parameters such as temperature, pH, and ion sensitivity, which allows the drug to be released gradually in a sustained manner. In-situ gelling system involves some advanced drug delivery which includes nanosuspension, nanoparticles, liposomes, niosomes, dendrimers, ocular iontophoresis, collagen shield, minidisc, ocular film, implants, Occusert, and many more examples of innovative dosage forms.

B. Anatomy of Eye:

The human eye is an extremely sensitive and intricate organ. Its anatomy is intriguing and complex. The human eye consists of 2 primary parts: the anterior chamber and Posterior chamber and the posterior chamber [4]. These two parts are the most important. The anterior part includes the tear film, cornea, pupil, lens, and ciliary body. The posterior area includes the conjunctiva, sclera, choroid, retina, vitreous fluid, and optic nerve. The epithelium layer is composed of several layers of tightly packed cells. The stroma is the dense layer filled with water, while the endothelium is vital in maintaining the cornea's transparency. The orbital glands and the secretory epithelial cells regulate the production and composition of tears. The front surface of the sclera is covered by the conjunctiva, a very thin and transparent membrane that lines the eyelids [5]. Three layers make up this mucosal membrane: are substanatia propria, which includes blood, lymphatic, and nerve vessels, and the outer epithelial layers [6], which attaches to the sclera, collagen and mucopolysaccharides make up the sclera, a continuous corneal layer. The vascular layer that marks

the choroid is located between the sclera and the retina. A thin layer of tissues covers the rear of the eye, called the retina [7, 8], which is made up of glial and neuronal cells [9] . It is in charge of producing electrical impulses that go to the brain through the optic nerve.

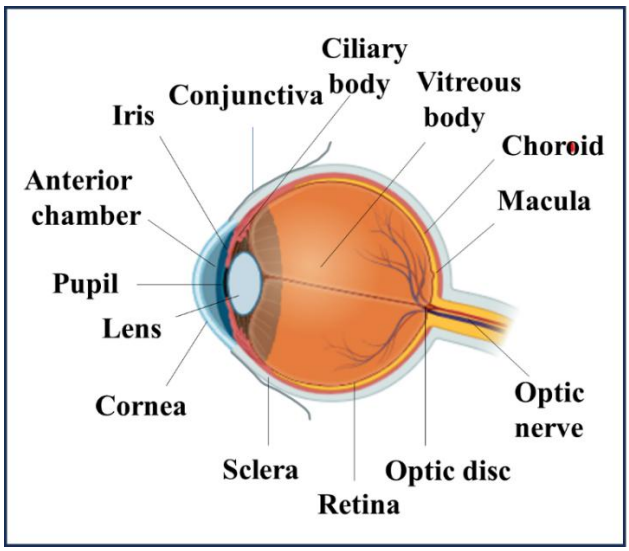

Figure 1: Anatomy of eye

C. Ocular Barriers

1. Precorneal barriers

The cul-de-sac describes the ocular obstacle [10]. It is a shallow pocket-like structure in the lower eyelid which forms in the deeper recess of the upper eyelid, and where the palpebral and bulbar conjunctiva meets. In people, the cul-de-sac maximum capacity is about 30 µL. Although this capacity can be lowered by 70-80% if the lower eyelid reverts to its natural position [11]. Furthermore, the cul-de-sac capacity may be further reduced by eye irritation and allergic reactions. Since the effectiveness of any medication is directly connected to its residence length and concentration, the cul-de-sac restricted capacity reduces drug concentration in the eye, which minimizes its therapeutic impact. Drug loss in the precorneal area from the lachrymal gland. The main obstacles in the pre-corneal space are the drainage of the ocular solution. drug absorption may also be further hampered by protein binding and drug metabolism. To keep the eyes hydrated and stop dust or infection from building up on the surface, tear fluid regeneration is essential.

2. Corneal Barrier

The cornea behaves as a robust barrier against various chemical and mechanical injuries and plays a vital role in focusing light onto the retina. It consists of layers: Epithelium, Stroma, and Endothelium [5]. The epithelium serves as an obstacle to the hydrophilic drugs and large molecules, while the stroma obstructs lipophilic drugs. Several other factors, such as mol wt., charge, degree of ionization, and hydrophobicity, etc., as a result trans transcorneal permeation is a rate-limiting step.

3. Blood-ocular barriers

This is categorized into two: blood aqueous barrier (BAB) and blood-retinal barrier (BRB). It prevents foreign particles from entering blood bloodstream [12]. BAB is the anterior part that restricts access to many substances from entering the intraocular environment[13]. It only allows lipophilic and small molecular weight drugs, which are eliminated more quickly from the anterior compartment [14] . Retinal pigment epithelial cells and endothelial cells comprise the BRB, a posterior region that keeps harmful substances, water, and plasma components out of the retina.

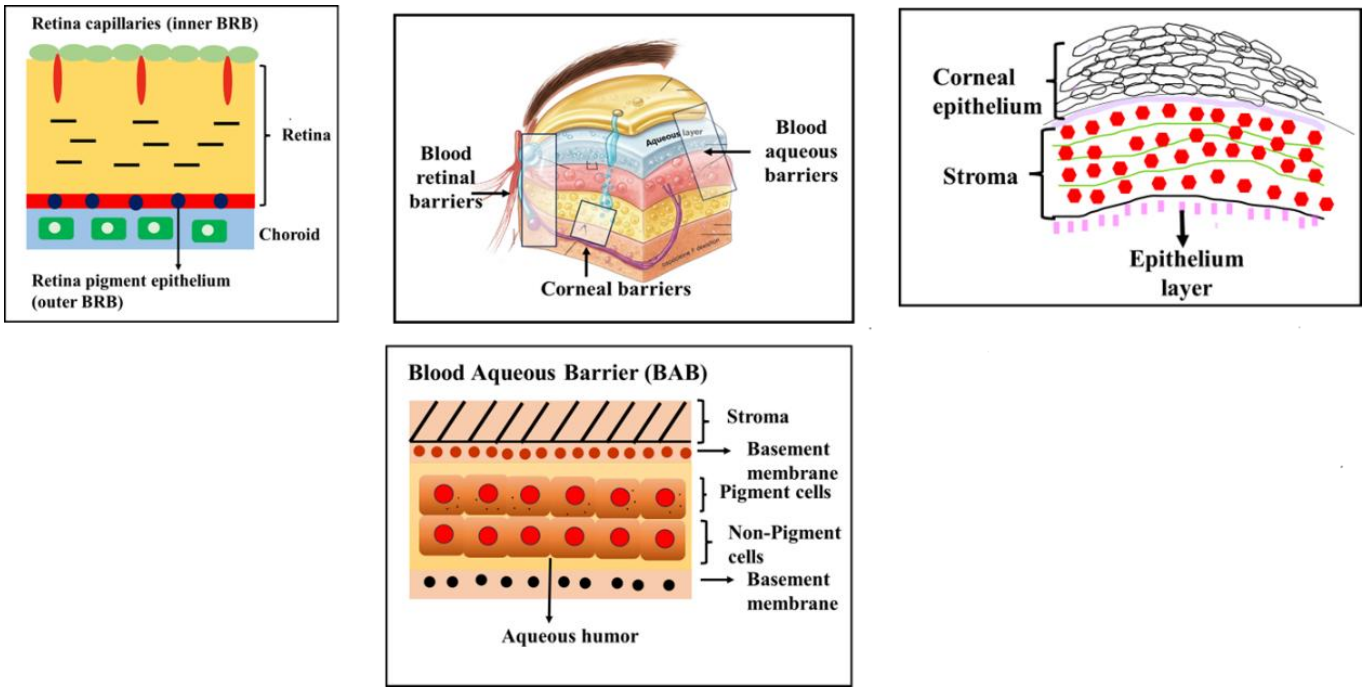

Figure 2: Ocular Barriers

D. Various routes of administration

1. Topical route

The topical route is the most common to administer the medicament 95% of marketed formulations follow the route. Although it is a nano-invasive method, its short residence time and inadequate corneal penetration result in a poor bioavailability(<5%) [15]. It results from the nasolacrimal pathways' absorption into the systemic circulation, blinking, and tear drainage [16]. This route requires frequent administration and high concentration, which can have significant side effects.

2. Intracameral Injections:

Intracameral injection involves directly injecting an antibiotic into the vitreous cavity. It is generally provided after cataract surgery.

3. Intravitreal Injections /Implants:

The intravitreal injection delivers the drug directly to the vitreous humor [17], which is located near to retina [17]. A new treatment approach for glaucoma [18] Involves a single intravitreal injection of vitamin E/polylactic/polylactic-co-glycolic acid microspheres [19] containing neurotrophic factor produced from glial cell lines [20].

4. Juxta Scleral Injection:

Juxta-scleral injections are used [21]. Conditions include trauma, diabetes-related illnesses, and cystoid macular edema benefit greatly from these injections. New treatment for age-related macular degeneration involves juxta-scleral injection of anecortave cortisone, which has demonstrated prolonged release over six months into the retina and choroid [22] .

5. Retrobulbar Route:

The retrobulbar method is administering medicine behind the eyeball into the retrobulbar space employing injection via the orbital fascia and eyelid [23]. Whenever amphotericin is given by this route, it exhibits more antifungal activity than intravenous injection when administered retrobulbar [24].

6. Subconjunctival Injection:

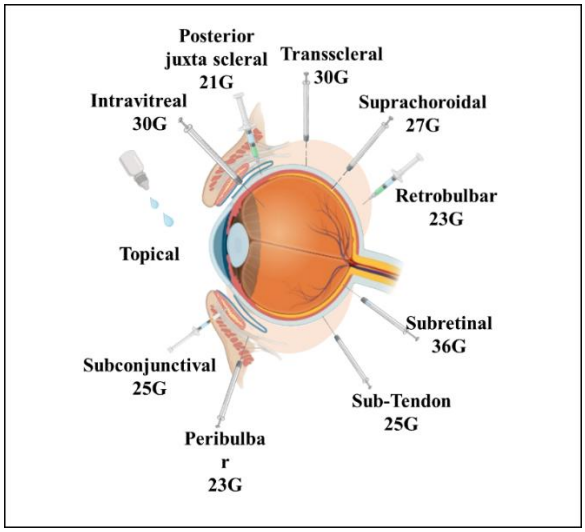

Figure 3: Various Ocular route of administration

Subconjunctival injection is given when topical treatment results in relatively little drug penetration into the anterior chamber of the eye. It is frequently utilized. For at least a month, the PEGylated liposomes have been used to. The administration of brinzolamide-encapsulated PLGA nanoparticles through subconjunctival injection effectively managed intraocular pressure for 10 days [25].

E. Ocular diseases

1. Cataract

Cataracts are the leading cause of vision loss globally, accounting for 40 to 60 percent of blindness worldwide due to complications [26]. According to the National Programme for Control of Blindness and Visual Impairment, cataracts cause 62.6% of instances of avoidable blindness in India [27]. Cataract develops cloudiness or opacification in the lens.

Glaucoma

A common optic neuropathy is glaucoma. Blurred vision is the first symptom, and in later stages, it may lead to permanent blindness [28]. It causes retinal ganglion cells to die and the optic nerve axons to gradually deteriorate, resulting in blindness. It is frequently linked to an increase in intraocular pressure due to abnormal aqueous fluid production or blockage. Open-angle and closed-angle glaucoma are the two types. Widening optic disc cupping and visual field loss due to increasing resistance to aqueous humor outflow through the trabecular meshwork are characteristic of open-angle glaucoma, which is often asymptomatic [29, 30].

Age-related Macular degeneration (AMD):

ADM is one of the main causes of vision loss in affluent countries. After the age of 50, it is more common. ADM causes around 8.7% of blindness globally. In 2020, around 196 million individuals had AMD, and by 2040, that figure is predicted to rise to 288 million[31]. It is a complicated degenerative disease that affects the posterior part of the eye [32]. AMD currently has no known cure, however, appropriate medicine may slow its development [33]. AMD comes in two varieties: Dry (atrophic or non-exudative) and wet (non-vascular or exudative). The primary feature of AMD is irregular angiogenesis, or the formation of new blood vessels, in the retinal epithelium, which leads to Bruch's membrane separation, atrophy, and drusen, or yellow deposits beneath the retina [33, 34].

2. Conjunctivitis:

Conjunctivitis is characterized by conjunctival irritation, which is very common. This condition can affect individuals of all ages, races, and genders [33]. Conjunctivitis can be classified as Infectious and non-infectious [35]. Infectious conjunctivitis occurs due to microbial infections, whereas non-infectious conjunctivitis is caused by allergens and irritants [36, 37]. Conjunctivitis symptoms include redness, pain, tears, and excessive eye secretion. the prevalence of allergic conjunctivitis is close to 40% worldwide [38].

3. Diabetic retinopathy:

Diabetes mellitus is a cause of Diabetic Retinopathy. All patients with diabetes type II will develop some degree of retinopathy after 20 years, and about 60% of individuals with type II diabetes will do the same. The main causes of diabetic retinopathy are inflammation and oxidative stress. These are caused by hyperglycemic conditions that cause pro-inflammatory mediators to be overexpressed [39]. Proliferative and non-proliferative diabetic retinopathy are the two primary forms. Both eventually cause the retina to deteriorate more and more. Nowadays, therapies for diabetic retinopathy include vitrectomy, laser, photocoagulation, and pharmaceutical measures [40]. Although treatment may leave scars, laser photocoagulation can stop blindness by closing leaky blood vessels [41].

4. Retinoblastoma:

Retinoblastoma, a malignant tumor that destroys the retina, mostly affects children under five if left untreated. 99% of cases result in blindness and finally death. Its frequency is about 1 out of 20,000 live births. The occurrence occurs at the same rate in both sexes. A mutation in the tumor suppressor gene RB1, which produces the protein retinoblastoma, is the cause of it. Both unilateral (60%) and bilateral (40%) are possible [42]. Retinoblastoma can be treated with radiation, cryotherapy, systemic chemotherapy, and surgery.

5. Fungal keratitis:

Fungal keratitis only develops with corneal damage because a healthy cornea would be impervious to infection by fungus [43]. Fungi Such as Candida albicans, Candida glabrata, Candida tropicalis, Candida krusei, and Candida parasitosis are the cause of fungal keratitis, which affects 40% of people worldwide. There are two types of risk factors for fungal keratitis: one is systemic and another is the eye. Leprosy, diabetes, and HIV-positive examples of systemic issues. complications from fungal keratitis include corneal ulceration, poor wound healing, and inflammation seeping into the corneal stroma. The corneal inflammation may alter miRNA expression [44].

F. Dosage Form

1. Liquid Dosage Forms

i. **Eye Drops:**

More than 95% of marketed eye medications are eye drops [45], which provides medicine to the front region of the eye. Their benefits include strong stability and ease of administration. Their limited retention period, poor bioavailability, and possibly dangerous side effects from regular usage of high concentrations are some of the major disadvantages.

ii. Eye suspension:

Ocular suspensions are a dispersion of hydrophobic drugs in an aqueous solution. These formulations enhance contact time by retaining the drug in the conjunctival cul-de-sac. Key factors during the preparation process include particle size, solubility, and dissolution rate in tear fluid. Generally, particles larger than 10 µm can cause ocular irritation and increased tearing. However, ocular suspensions have some disadvantages, including poor stability.

iii. Eye Emulsion:

An emulsion is a biphasic system maintained in a stable form with the help of surfactants or stabilizing agents [46]. The capacity to administer hydrophobic medications is one of the benefits of ocular emulsion. In addition, oil-in-water emulsion improves bioavailability, provides longer contact durations, and is less ocular irritating.

2. Semisolid Dosage Forms

i. Eye gel:

Eye gels have a higher water content and are semisolid dose formulations. Their increased viscosity enhances retention time and bioavailability, although they can still cause blurred vision [47]. Different polymers can be utilized to formulate ocular gels, such as Polyacrylic acid, acrylic acid, hydroxypropyl methylcellulose, and carboxymethyl cellulose [48]. Curcumin-containing proniosomal gel was prepared using the coacervation approach, which resulted in a notable reduce size of particles and an increase in anti-inflammatory activity [49]. Moreover, a phytantriol-based liquid crystalline gel using a vortex process increased retention time [50]

iv. **Eye Ointment:**

Eye ointments are semisolid dosage forms made of mineral oil and white petroleum. Due to their potential to impair eyesight, they are exclusively administered to the lower eyelid at night [45]. These ointments are frequently used in young patients and are anhydrous, making them appropriate for Drugs that are moisture-sensitive and lipophilic. They also show a longer residence period and greater Bioavailability than solution.

3. Solid dosage forms

i. Occusert Inserts:

Ocular inserts are solid dosage forms with a zero-order drug release mechanism that are composed of biodegradable polymers [51]. Longer residence time, continuous medication delivery, steady release rates, and fewer adverse effects are some advantages of these inserts [52]. Triamcinolone acetonide-infused nanofibers were produced using the electrospinning method. These nanofibers exhibited smaller particle sizes, enhanced systemic absorption, and minimized side effects.

ii. Therapeutic Contact Lens:

According to recent research, therapeutic contact lenses' prolonged residence duration and close contact with the cornea can increase medication absorption by more than 50%. They have a ten-fold longer residence period than traditional eye drops. These lenses decrease the necessary dosage, the time between dosages, and systemic absorption. There are several methods for encapsulating the medication in contact lenses, such as soaking, ion ligation, molecular imprinting, and the application of nanoparticles [53]. However, several issues, including protein attachment, ion and oxygen

permeability, medication loss during production or storage, light transmittance, and lens swelling, make it difficult to employ them clinically [54].

G. Benefits of the in-situ gelling method over traditional ocular formulation:

1. Extended Residence time
2. Enhanced bioavailability.
3. Reduced systemic absorption
4. Accurate drug delivery
5. Improved therapeutic efficacy

H. Disadvantages of in-situ gels:

1. Required an appropriate amount of tear fluid.
2. The drug present in the solution may degrade.
3. Chemical degradation leads to stability issues [55].
4. Only a small dose can be administered.
5. Low mechanical strength leads to premature dissolution.

I. Types of In-situ gelling systems

1. pH-sensitive in-situ gelling system:

The physiological environment's pH shift causes the sol-to-gel transition. Pendant acidic or basic groups found in pH-sensitive polymers can either receive or release a proton in response to pH changes. Polyelectrolytes are polymers that contain a lot of ionizable groups. Anionic groups in weakly acidic polymers cause swelling when the pH rises, although edema falls in weakly basic medications. When designing the ophthalmic drops, the buffer is crucial. They have a major impact on clinical response and chemical stability. They also affect the product's safety and comfort. Gelling brought on by a pH shift is one of the possible ophthalmic in situ gels described in the literature [56]. The polymers that show pH-responsive in-situ gelling are as follows: hydroxypropyl methylcellulose (HPMC), polyacrylic acids, cellulose acetate, etc. These are stable, non-irritating, and offer sustained release of the medication [48].

2. Temperature sensitivity in-situ gelling system:

The formulation is liquid at room temperature (20- 250 °C), but when it comes into contact with the application site (35- 37 °C), the temperature rises and it becomes a gel. There is a volume phase transition in temperature-sensitivity hydrogels at certain higher critical solution temperatures (UCST) or lower critical solution temperatures (LCST) [57]. The sol–to–gel transformation mechanism is based on the progressive desolvation of the polymer with increasing temperature, which causes the polymeric network to become more entangled and aggregate into micellar. The dehydration of the polyoxypropylene block leads to the production of micelles. After coming into contact, the micelles lose their freedom of motion.

3. Ion active sensitive in situ-gelling system:

The ion active gelling system is a solution initially, and when it comes in contact with the tear fluid of the eye instantly converts into a gel. There is a variety of ion-responsive gelling agents as follows: Gellan gum, sodium alginate undergoes cross-linking with the ions, and so that the gel is formed. Ion ion-activated in-situ gelling system provides extended retention time in the ocular, which increases patient compliance [58].

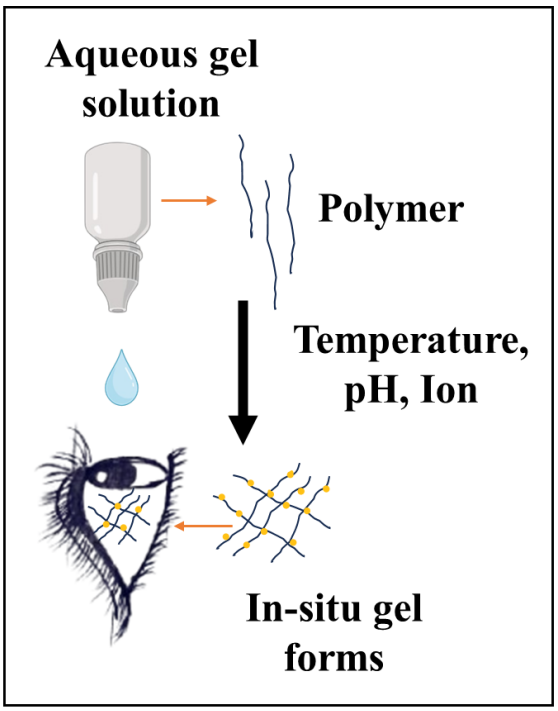

Figure 4: Typical Mechanism of ocular in-situ gel

J. Benefits of the in-situ gelling method containing nanoparticles:

Ocular in-situ nanogels are better than other drug delivery methods for eye diseases. They improve the drug's bioavailability [59]. The gel's nanoparticles ' size makes it easier for drugs to enter the tissues of the eyes, increasing concentrations of medication at the desired place [60]. Ocular in-situ nanogels are additionally used to regulate drug release medications gradually, extending the therapeutic concentration at a specific location, in contrast to ocular drops, which may remove medications rapidly [61]. A contrast supply of drugs is required for chronic eye disorders. Ophthalmic in-situ nanogels are easy to use for doctors [62]. Because they are biocompatible and biodegradable, they do not cause toxicity or unpleasant responses. Ocular in-situ therapy is one potential way to provide medication for eye disorders [63].

K. Types of nanoparticles:

1. Liposomes:

Liposomes provide several benefits, including increased bioavailability, safety, biodegradability, and ease of manufacturing [64]. One or more concentric lipid bilayers make up these spherical nanocarriers. Liposomes can transport hydrophilic medications in their central core and lipophilic medications in their lipid layer. The formation procedure and composition may be changed to

change their temperature responsiveness, surface charge, sensitivity to ions or pH, and ultimately particle size. Since the corneal epithelium typically has a negative charge, using liposomes that are positively charged can improve absorption and extend retention duration.

2. Niosomes:

Niosomes are nano-ionic surfactants that self-aggregate in two layers, which are nanocarriers. They can contain both hydrophilic and lipophilic medications without inciting an immunological reaction, and they are biodegradable and biocompatibility [65]. Niosomes can increase and extend the release of drugs. However, it shows drawbacks, including the possibility for hydrolysis, chemical instability, and drug loss or buildup. Cholesterol or its derivatives are frequently added to niosomes to increase their stiffness and stability.

3. Nanoemulsion:

Nanoemulsions might be used as delivery systems for the eyes. Oil-in-water nanoemulsions are composed of a dispersed oil phase stabilised by surfactants in an aqueous medium [66]. These nanoemulsion interacts with the lipids in tears and act as a reservoir for lipophilic medications. Provides prolonged release [67]. Because they interact with the corneal surface and improve medication solubility, surfactants are essential. however, employing Nanoemulsions creates a milky solution, and decreased tolerance to eye irritation brought on by elevated amounts of surfactants might result in impaired vision if the size of the particle exceeds 100nm.

4. Nanosuspension:

Lipophilic drugs dispersed in a mixture of media maintained by polymer or surfactants make up colloidal nanocarriers. Its advantages are enhanced solubility and bioavailability, longer residence time, and prolonged drug release [68]. among the most Eudragit® polymers are often used mucoadhesive agents in nanosuspensions [69].

5. Nano micelles:

Nanocarriers are anionic, cationic, or zwitterionic surfactants that make up nanocarriers, which can be spherical, cylindrical, or star-shaped, among other shapes. Both hydrophilic and lipophilic medications can be encapsulated in these carriers [70]. These carriers have simple preparation methods that lead to better drug penetration, higher bioavailability, decreased toxicity, and increased stability [71]. They are capable of delivering drugs to both the anterior and posterior segments of the eye [72].

6. Polymeric nanoparticles:

Based on their shape and technique of synthesis, polymeric nanoparticles may be divided into two types: nanospheres and nanocapsules. Small, solid spheres made of a dense network of polymers are called nanospheres. Their matrix-like structure provides a lot of surface area, enabling medications to get trapped inside the particles or absorbed onto their surface. Nano capsules, on the other hand, are made up of tiny liquid cores encapsulated in a polymeric membrane like nanospheres. Medications can be encapsulated within the liquid core of the capsule or adsorbed onto its surface. Because of their tiny particle size, these polymeric nanoparticles may reach both eye segments, improving patient compliance, especially when controlling chronic illness. They provide better penetration, extended drug release, and decreased elimination.

7. Solid lipid nanoparticles (SLNs):

Drugs that are lipophilic and hydrophilic are encapsulated in solid lipid nanoparticles, which are made up of a solid lipid matrix. Triglycerides, fatty acids, steroids, and waxes are common lipids employed to make these nanoparticles [73, 74]. One of the SLN's main benefits is that they don't need surfactant can stabilize lipid dispersion in place of organic solvents. Furthermore, the production of SLNs is economical, safe, biodegradable, and biocompatible.

8. Nanostructure Lipid Carriers:

Although being a second-generation lipid nanoparticles, which contain around 30% liquid lipids, the final product is solid and does not have a crystalline structure [75]. The content is higher than with solid lipid nanoparticles because the liquid oil droplets provide the drug with additional space in the lipid matrix. Low toxicity, improved effectiveness, and controlled release are all displayed by these nanoparticles.

9. Nanocrystals:

The main component of the medication is nanocrystals, which are stabilized and encased by a variety of excipients. Small particle size, simple production methods, strong mucoadhesive qualities, and improved bioavailability are some of the characteristics of these nanocrystals [76]. Nanocrystals are considered potential nanocarriers deserving of immediate further research [77].

10.Dendrimers:

Dendrimers are three-dimensional structures of repeating molecular units that surround a central core and are extremely branched, star-shaped, tree-shaped, or tree-shaped [78]. Because of their many terminal functionalities, they can be used to deliver both hydrophilic and lipophilic medications [79]. Its benefits include longer residence time, enhanced bioavailability, targeted distribution, extended activity, and antibacterial qualities have all been shown for dendrimers. They can provide drugs to both eye segments.

11.Cubosomes:

Lipids are emulsified in water with a stabilizer from bicontinuous cubic liquid crystalline nanocarriers known as cubosomes [80]. Because of their vast surface area, they can encapsulate a large number of medications and are stable, easy to produce, biodegradable, and generally safe.

12.Olaminosomes:

The primary constituents of the olaminosomes are a surfactant, oleic acid, and Oleylamine. A common option for manufacturing ocular nanocarriers is oleic acid, a naturally occurring unsaturated fatty acid that is safe and biodegradable. Oleic acid is the source of Oleylamine, an

unsaturated fatty amine that is widely utilized as a surfactant or co-stabilizer. It includes tiny particles, high drug entrapment capabilities, improved corneal penetration, and general safety and efficiency.

size, sufficient zeta potential, favourable safety profiles, greater corneal penetration, higher activity, and high drug entrapment capabilities [81]. Abdelbary and associates create terconazole-infused edge activators,

13.Bilosomes:

Bilayered nanocarriers called bilosomes are made up of bile salts. They feature a tiny particle

span 60, and cholesterol to create bilosomes. Superior drug entrapment, higher activity, and better permeability we all displayed by the final formulation [82].

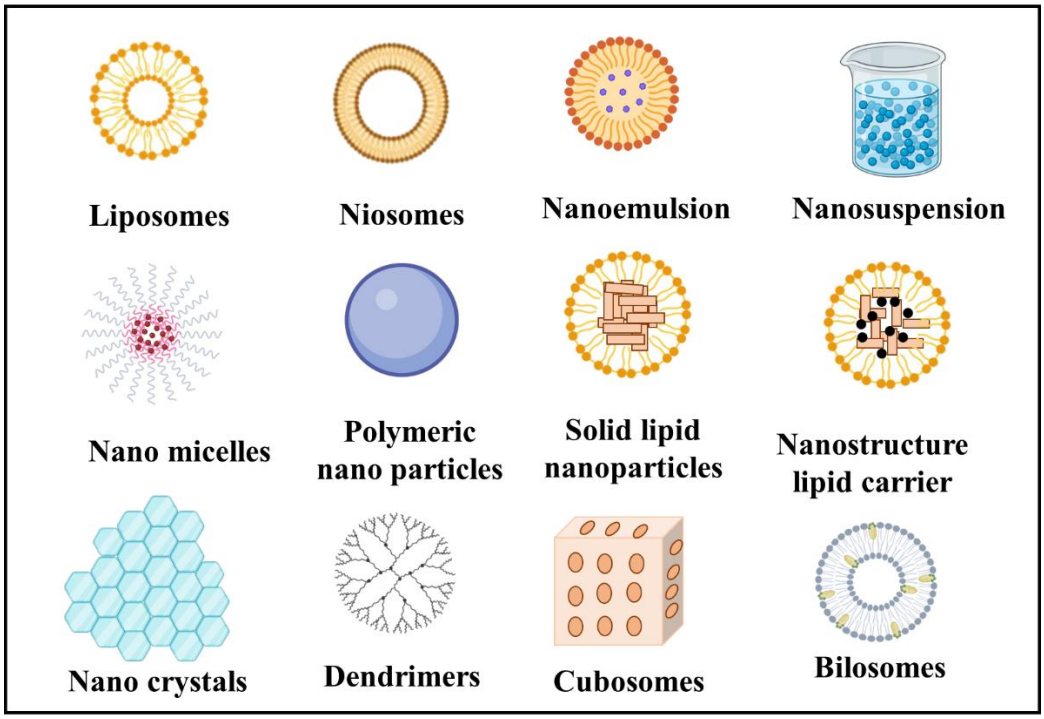

Figure 5: Various types of Nanoparticles

Table 1: Characterization of nanoparticles loaded in-situ gelling system:

Parameter	Description	Procedure
pH Measurement	pH impacts drug stability, permeation, and ocular comfort. Formulations with very low (<4) or high (>10) pH can irritate the eye.	Ideal pH range: 4–8 (enhances permeation, avoids irritation). Measured using a digital pH meter. Ocular formulation pH typically falls between 3.50 and 8.50 [83].
Visual Appearance	Influenced by particle size, oil type, and surfactant. Important for product appeal and user compliance.	Nano formulations may appear transparent, translucent, or turbid. % Transmittance measured using UV spectroscopy to assess clarity [84].
Gelling Ability	Indicates the ability of sol to transform into gel in a lachrymal fluid.	A drop of formulation is added to 2 mL of simulated tear fluid. Gelation is visually observed [58].
Osmolarity	Important for ocular comfort. Osmolarity imbalances can cause irritation or damage.	Normal tear osmolarity: 231–446 mOsm/kg. Values <100 or >640 mOsm/kg may cause discomfort. Takes into account vapor pressure, freezing/boiling point, and osmotic pressure [85].
Rheological Studies	Determines viscosity and flow behaviour before and after gelation, critical for in-situ gels.	Measured using a Brookfield viscometer. Before gelation: 5–1000 mPa·s After gelation: 50–50000 mPa·s At Temperature: 25°C (before), 37±0.05°C (after) [86]

In Vitro Drug Release	Simulates drug release into the eye to evaluate performance.	Conducted using a Franz diffusion cell with dialysis membrane (0.22 µm pore). Receptor: Simulated tear fluid Donor: Formulation Assembly kept at 37±0.5°C on magnetic stirrer. Sample analyzed by UV spectrophotometer [87].
Texture Analysis	Determines gel's mechanical properties, indicating patient acceptability.	Done using Texture Analyzer to assess cohesion, stiffness, and consistency. High adhesiveness indicates better contact with the eye surface [88].
Isotonicity Testing	Ensures osmotic balance with tears to prevent irritation or cell damage.	Formulations are mixed with drops of blood and observed under a 45x microscope. Compared with commercial ophthalmic products for isotonic behaviour [89]
Compatibility & Melting Point Studies	Detects drug-polymer interactions and thermal properties.	FTIR (Fourier Transform Infrared Spectroscopy): for interaction via the KBr pellet method. DSC (Differential Scanning Calorimetry): for phase transition/thermal shifts. TGA (Thermogravimetric Analysis): for water content determination [90].
Stability Studies	Checks shelf-life, formulation robustness under storage.	Short-term accelerated stability (ICH guidelines) Storage: 40±2°C, 75±5% RH Parameters: drug release, drug content, viscosity, clarity, pH, gelling capacity, tested weekly [91].
Size and Uniformity Analysis	Determines nanoparticle size and distribution uniformity.	Conducted through Dynamic Light Scattering (DLS) using instruments like Zetasizer. Particle size (PS) and Polydispersity Index (PDI) were measured. PDI = 0 (uniform), PDI = 1 (non-uniform) [92].
Zeta Potential (ZP)	Indicates physical stability and ability to interact with the ocular surface.	Measured through electrophoretic mobility. ZP: ±20 mV is considered to be ideal and leads to stability [93].
Drug Distribution	Determines how well the drug is incorporated and retained in the system.	% Entrapment Efficiency (%EE): Drug entrapped relative to total drug used. % Drug Loading (%DL): Drug mass relative to system mass. Affected by the drug's hydrophobicity, MW, and carrier material properties [94].
Ocular Biocompatibility (Hen's Egg Test)	Evaluates the irritation potential of the formulation.	Uses Hen's Egg Chorioallantois Membrane (HET-CAM) assay. Fertilized eggs were incubated at 37±0.5°C, 67±5% RH for 10 days. Observed for hemorrhage, clotting, hyperemia. Confirms ocular safety [95].

Table 2: Ocular in-situ Gels approved for market

Product name	Polymers used	Types of in-situ gel systems	Company name
Akten	Hydroxypropyl methyl cellulose	Temperature active [96]	Akorn Operating Company
Azasite	Poloxamer407	Temperature active [97]	InSite Vision
Pilocarpine-HS	Poloxamer407	pH active [97]	

Table 3: Patents of Ocular in-situ gels

Patent no.	Patent Title	Gelling agents
US 2011/0082 128 A1	Ocular medication delivery system using in-situ gel	Deacetylated gellan gum [98]
US 2002/0 114 778 A1	Reversible gelling technique	Propylene oxide, ethylene oxide with Hydroxy propyl methyl cellulose [120].
WO 2 011 018 800 A3	In-situ gel for ocular delivery	A blend of Thermoreversible natural polysaccharide polymer [99, 100].
US 6 703 039 B2	Reversible gelling technique	Propylene oxide and ethylene oxide with hydroxy propyl methyl cellulose US 6 703 039 B2 [101]

Table 4: Reported nanoparticles loaded in-situ gelling system

APIs	Polymer	Type of stimuli	Major Findings
Curcumin	Kolliphor 188 and 407	Thermo-active nanostructured lipid carriers	Noticeably improved preocular retention time. [97]
Dorzolamide	Pluronic 407	Thermo-active nanoemulsion	Non-irritating and extremely therapeutically effective. [102]
Ketorolac	Poloxamer@F-127 and hydroxypropyl methylcellulose	Thermo-active nanoemulsion	Enhanced drug release, ocular bioavailability, and no irritation [103]
Loteprednol	Pluronic-407and 188	Ion-Active nanoemulsion	Increase residence time,2,54 times bioavailability. [104]
Timolol	Gelerite	Ion-Active Liposomes	Low intraocular pressure and more effective. [105]

Table 5: Reported multi-stimuli responsive in-situ gels

API	Polymers	Response	Results
Ciprofloxacin	Carbomer	pH and thermo-responsive	Increased effectiveness of treatment and provides 8 hr of prolonged-release [100]
Levofloxacin	Algin and chitin	Ions and pH-responsive	Retention time was improved [106]
Nepafenac	Chitosan N-(carboxymethyl) and pluronic	pH and thermo-responsive	Gellation was on 32-33°C [107]
Sparfloxacin	Algin and Chitin	Ion and pH-responsive	Rapid gelation occurs at pH 7.4 and prolonged release for 24 hrs [106]
Timolol	Chitin with gellan gum	pH and ion-responsive	Improved corneal penetration and prolonged drug release.[105]

L. Conclusion:

Effective drug delivery to the eyes is the most challenging due to various natural barriers, like tear drainage and limited absorption. Traditional methods like drops and injections have limitations, such as short retention time and potential side effects. To overcome these issues, advanced drug delivery systems like in-situ gels, nanoparticles, and nanocarriers have been developed. These modern approaches improve drug retention, bioavailability, and patient comfort by promising controlled and sustained release. In-situ gels are particularly promising as they transform into a gel upon contact with the eye, extending drug retention and minimizing the need for frequent dosing. With continuous advancements in nanotechnology and smart drug delivery systems, the future of ocular drug treatment looks promising, offering efficiency and improved patient care.

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References

1. Vyas U, Gehalot N, Jain V, Mahajan S. A Review on in situ gelling system for ophthalmic drug delivery. Current Research in Pharmaceutical Sciences. 2021:98-106. https://doi.org/10.24092/CRPS.2021.110402

2. Lynch CR. Development and characterization of a solid lipid nanoparticle-loaded thermosensitive gel for the delivery of timolol to the eye: Department of Ophthalmology, Faculty of Health Sciences, University of the ...; 2022.

3. Wu KY, Joly-Chevrier M, Akbar D, Tran SD. Overcoming Treatment Challenges in Posterior Segment Diseases with Biodegradable Nano-Based Drug Delivery Systems. Pharmaceutics. 2023;15(4):1094. https://doi.org/10.3390/pharmaceutics15041094 PMid:37111579 PMCid:PMC10142934

4. Bertelli E. Anatomy of the eye and human visual system: Piccin Nuova Libraria spa; 2019.

5. Nishida T, Saika S, Morishige N. Cornea and sclera: anatomy and physiology. Cornea. 2017;1:1-22. https://doi.org/10.1097/ICO.0000000000001342 PMid:28902015

6. Dua HS, Said DG. Ocular Surface Epithelium: Applied Anatomy. Corneal Regeneration: Therapy and Surgery. 2019:175-90. https://doi.org/10.1007/978-3-030-01304-2_12

7. Angayarkanni N, Coral K, Bharathi Devi SR, Saijyothi AV. The biochemistry of the eye. Pharmacology of Ocular Therapeutics. 2016:83-157. https://doi.org/10.1007/978-3-319-25498-2_5

8. Reh TA. The development of the retina. Ryan's Retina E-Book. 2017:375.

9. Reichenbach A, Bringmann A. Glia of the human retina. Glia. 2020;68(4):768-96. https://doi.org/10.1002/glia.23727 PMid:31793693

10. Ahmed S, Amin MM, Sayed S. Ocular drug delivery: a comprehensive review. AAPS PharmSciTech. 2023;24(2):66. https://doi.org/10.1208/s12249-023-02516-9 PMid:36788150

11. Zeno R, Teall AM. Evidence-Based Assessment of the Eyes. Evidence-Based Physical Examination: Best Practices for Health and Well-Being Assessment. 2024:367. https://doi.org/10.1891/9780826155320.0015

12. Ranganath SH, Thanuja M, Anupama C, Manjunatha T. Systemic drug delivery to the posterior segment of the eye: Overcoming blood-retinal barrier through smart drug design and nanotechnology. Immobilization Strategies: Biomedical, Bioengineering and Environmental Applications. 2021:219-69. https://doi.org/10.1007/978-981-15-7998-1_6

13. Diwan P, Jangde R, Khunte S, Bhardwaj H, Suresh PK. Ocular drug delivery system: barrier for drug permeation, method to overcome barrier. Drug Development Life Cycle: IntechOpen; 2022. https://doi.org/10.5772/intechopen.105401

14. Mofidfar M, Abdi B, Ahadian S, Mostafavi E, Desai TA, Abbasi F, et al. Drug delivery to the anterior segment of the eye: A review of current and future treatment strategies. International journal of pharmaceutics. 2021;607:120924. https://doi.org/10.1016/j.ijpharm.2021.120924 PMid:34324989 PMCid:PMC8579814

15. Panda P, Mohanty S, Gouda SR, Mohapatra R. Advances in Nanomedicine for Retinal Drug Delivery: Overcoming Barriers and Enhancing Therapeutic Outcomes. Journal of Drug Targeting. 2024(just-accepted):1-49. https://doi.org/10.1080/1061186X.2024.2443144 PMid:39694681

16. Khode PD, Dongare PA. In situ gel: A Review of Pharmaceutical and Biological Evaluation and Approaches. Research Journal of Pharmaceutical Dosage Forms and Technology. 2019;11(3):217-26. https://doi.org/10.5958/0975-4377.2019.00037.5

17. Mishra D, Gade S, Glover K, Sheshala R, Singh TRR. Vitreous humor: composition, characteristics and implication on intravitreal drug delivery. Current eye research. 2023;48(2):208-18. https://doi.org/10.1080/02713683.2022.2119254 PMid:36036478

18. Shalaby WS, Shankar V, Razeghinejad R, Katz LJ. Current and new pharmacotherapeutic approaches for glaucoma. Expert Opinion on Pharmacotherapy. 2020;21(16):2027-40. https://doi.org/10.1080/14656566.2020.1795130 PMid:32717157

19. Agrahari V, Agrahari V, Hung W-T, Christenson LK, Mitra AK. Composite nanoformulation therapeutics for long-term ocular delivery of macromolecules. Molecular pharmaceutics. 2016;13(9):2912-22. https://doi.org/10.1021/acs.molpharmaceut.5b00828 PMid:26828415

20. García-Caballero C, Prieto-Calvo E, Checa-Casalengua P, García-Martín E, Polo-Llorens V, García-Feijoo J, et al. Six month delivery of GDNF from PLGA/vitamin E biodegradable microspheres after intravitreal injection in rabbits. Eur J Pharm Sci. 2017;103:19-26. https://doi.org/10.1016/j.ejps.2017.02.037 PMid:28259830

21. Gorantla S, Rapalli VK, Waghule T, Singh PP, Dubey SK, Saha RN, et al. Nanocarriers for ocular drug delivery: Current status and translational opportunity. RSC advances. 2020;10(46):27835-55. https://doi.org/10.1039/D0RA04971A PMid:35516960 PMCid:PMC9055630

22. Shelley H, Annaji M, Grant M, Fasina O, Babu RJ. Sustained release biodegradable microneedles of difluprednate for delivery to posterior eye. Journal of Ocular Pharmacology and Therapeutics. 2022;38(6):449-58. https://doi.org/10.1089/jop.2021.0089 PMid:35167767

23. Mitchcell N, Oliver J. Feline Ophthalmology. The manual: Grupo Asís Biomedia SL; 2021.

24. Spiess BM. Ophthalmic Pharmacology. Ophthalmic Disease in Veterinary Medicine: CRC Press; 2018. p. 39-75. https://doi.org/10.1201/b20810-2

25. Zhou X, Zhou D, Zhang X, Liao L, Wu P, Chen B, et al. Research progress of nano delivery systems for intraocular pressure lowering drugs. Heliyon. 2024. https://doi.org/10.1016/j.heliyon.2024.e32602 PMid:39005914 PMCid:PMC11239466

26. Sheppard J, Garg S, Lievens C, Brandano L, Wirostko B, Korenfeld M, et al. Iontophoretic dexamethasone phosphate compared to topical prednisolone acetate 1% for noninfectious anterior segment uveitis. American Journal of Ophthalmology. 2020;211:76-86. https://doi.org/10.1016/j.ajo.2019.10.032 PMid:31726034

27. Rajan S, Sathiyanarayanan M, Prashant S, Prashant S, Nataraj P, editors. Prevention of avoidable blindness and improving eye healthcare system in india. 2018 10th International Conference on Communication Systems & Networks (COMSNETS); 2018: IEEE. https://doi.org/10.1109/COMSNETS.2018.8328292

28. Marjanovic I. The optic nerve in glaucoma. The Mystery of Glaucoma. 2011. https://doi.org/10.5772/19811

29. Umezurike BC, Akhimien MO, Udeala O, Green UG, Okpechi-Agbo U, Ohaeri MU. Primary open angle glaucoma: the pathophysiolgy, mechanisms, future diagnostic and therapeutic directions. Ophthalmology Research: An International Journal. 2019;10(3):1-17. https://doi.org/10.9734/or/2019/v10i330106

30. Weinreb RN, Leung CK, Crowston JG, Medeiros FA, Friedman DS, Wiggs JL, et al. Primary open-angle glaucoma. Nature reviews Disease primers. 2016;2(1):1-19. https://doi.org/10.1038/nrdp.2016.67 PMid:27654570

31. Korva-Gurung I. Neovascular age-related macular degeneration: incidence, prevalence, treatment outcomes and quality of life. 2024.

32. Deng Y, Qiao L, Du M, Qu C, Wan L, Li J, et al. Age-related macular degeneration: Epidemiology, genetics, pathophysiology, diagnosis, and targeted therapy. Genes & diseases. 2022;9(1):62-79. https://doi.org/10.1016/j.gendis.2021.02.009 PMid:35005108 PMCid:PMC8720701

33. Hernández-Zimbrón LF, Zamora-Alvarado R, Ochoa-De la Paz L, Velez-Montoya R, Zenteno E, Gulias-Cañizo R, et al. Age-related macular degeneration: new paradigms for treatment and management of AMD. Oxidative medicine and cellular longevity. 2018;2018(1):8374647. https://doi.org/10.1155/2018/8374647 PMid:29484106 PMCid:PMC5816845

34. Joseph A. Tissue characteristics in retinal surface disorders: University of Split. School of Medicine. Ophthalmology; 2019.

35. Shivaji S. Antimicrobial Resistance of the Diseased Human Eye: Conjunctivitis. Antimicrobial Resistance of the Human Eye: CRC Press. p. 372-417. https://doi.org/10.1201/9781003451105-13

36. Azari AA, Arabi A. Conjunctivitis: a systematic review. Journal of ophthalmic & vision research. 2020;15(3):372. https://doi.org/10.18502/jovr.v15i3.7456 PMid:32864068 PMCid:PMC7431717

37. Mukherjee P, Bandyopadhyay P. Infectious Diseases of the Eye: Wolters kluwer india Pvt Ltd; 2020.

38. Dupuis P, Prokopich CL, Hynes A, Kim H. A contemporary look at allergic conjunctivitis. Allergy, Asthma & Clinical Immunology. 2020;16:1-18. https://doi.org/10.1186/s13223-020-0403-9 PMid:31993069 PMCid:PMC6975089

39. Nalini M, Raghavulu B, Annapurna A, Avinash P, Chandi V, Swathi N. Correlation of various serum biomarkers with the severity of diabetic retinopathy. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2017;11:S451-S4. https://doi.org/10.1016/j.dsx.2017.03.034 PMid:28420575

40. Mansour SE, Browning DJ, Wong K, Flynn Jr HW, Bhavsar AR. The evolving treatment of diabetic retinopathy. Clinical Ophthalmology. 2020:653-78. https://doi.org/10.2147/OPTH.S236637 PMid:32184554 PMCid:PMC7061411

41. Global estimates on the number of people blind or visually impaired by glaucoma: A meta-analysis from 2000 to 2020. Eye. 2024:1-11.

42. Soliman SE, Racher H, Zhang C, MacDonald H, Gallie BL. Genetics and molecular diagnostics in retinoblastoma-an update. The Asia-Pacific Journal of Ophthalmology. 2017;6(2):197-207.

43. Donovan C, Arenas E, Ayyala RS, Margo CE, Espana EM. Fungal keratitis: Mechanisms of infection and management strategies. Survey of ophthalmology. 2022;67(3):758-69. https://doi.org/10.1016/j.survophthal.2021.08.002 PMid:34425126 PMCid:PMC9206537

44. Boomiraj H, Mohankumar V, Lalitha P, Devarajan B. Human corneal microRNA expression profile in fungal keratitis. Investigative ophthalmology & visual science. 2015;56(13):7939-46. https://doi.org/10.1167/iovs.15-17619 PMid:26720440

45. Maulvi FA, Shetty KH, Desai DT, Shah DO, Willcox MD. Recent advances in ophthalmic preparations: Ocular barriers, dosage forms and routes of administration. International journal of pharmaceutics. 2021;608:121105. https://doi.org/10.1016/j.ijpharm.2021.121105 PMid:34537269

46. Gibson M. Ophthalmic dosage forms. Pharmaceutical preformulation and formulation: CRC Press; 2016. p. 443-67. https://doi.org/10.3109/9781420073188-15 PMCid:PMC5154371

47. Rahić O, Tucak A, Omerović N, Sirbubalo M, Hindija L, Hadžiabdić J, et al. Novel drug delivery systems fighting glaucoma: Formulation obstacles and solutions. Pharmaceutics. 2020;13(1):28. https://doi.org/10.3390/pharmaceutics13010028 PMid:33375224 PMCid:PMC7824381

48. 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. https://doi.org/10.3390/ph14111201 PMid:34832983 PMCid:PMC8621906

49. Dargude S, Dhake P, Hole A, Pinjari RR, Hingne S. A REVIEW ON CURCUMIN LOADED NANO DRUG DELIVERY SYSTEMS: NANO FORMULATIONS AND RECENT ADVANCES.

50. Wang X, Zhang Y, Huang J, Tian C, Xia M, Liu L, et al. A novel phytantriol-based lyotropic liquid crystalline gel for efficient ophthalmic delivery of pilocarpine nitrate. AAPS PharmSciTech. 2019;20:1-14. https://doi.org/10.1208/s12249-018-1248-0 PMid:30603986

51. Mariz M, Murta J, Gil M, Ferreira P. An ocular insert with zero-order extended delivery: release kinetics and mathematical models. European Journal of Pharmaceutics and Biopharmaceutics. 2022;181:79-87. https://doi.org/10.1016/j.ejpb.2022.10.023 PMid:36351492

52. 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. https://doi.org/10.1016/j.cis.2020.102342 PMid:33444845

53. Trujillo-de Santiago G, Sharifi R, Yue K, Sani ES, Kashaf SS, Alvarez MM, et al. Ocular adhesives: Design, chemistry, crosslinking mechanisms, and applications. Biomaterials. 2019;197:345-67. https://doi.org/10.1016/j.biomaterials.2019.01.011 PMid:30690421 PMCid:PMC6687460

54. Chaudhari P, Ghate VM, Lewis SA. Next-generation contact lenses: Towards bioresponsive drug delivery and smart technologies in ocular therapeutics. European Journal of Pharmaceutics and Biopharmaceutics. 2021;161:80-99. https://doi.org/10.1016/j.ejpb.2021.02.007 PMid:33607239

55. Kempe S, Mäder K. In situ forming implants-an attractive formulation principle for parenteral depot formulations. Journal of controlled release. 2012;161(2):668-79. https://doi.org/10.1016/j.jconrel.2012.04.016 PMid:22543012

56. Kushwaha SK, Saxena P, Rai A. Stimuli sensitive hydrogels for ophthalmic drug delivery: A review. International journal of pharmaceutical investigation. 2012;2(2):54. https://doi.org/10.4103/2230-973X.100036 PMid:23119233 PMCid:PMC3482766

57. Taylor MJ, Tomlins P, Sahota TS. Thermoresponsive gels. Gels. 2017;3(1):4. https://doi.org/10.3390/gels3010004 PMid:30920501 PMCid:PMC6318636

58. Ahmed B, Jaiswal S, Naryal S, Shah RM, Alany RG, Kaur IP. In situ gelling systems for ocular drug delivery. Journal of Controlled Release. 2024;371:67-84. https://doi.org/10.1016/j.jconrel.2024.05.031 PMid:38768662

59. Liu R, Sun L, Fang S, Wang S, Chen J, Xiao X, et al. Thermosensitive in situ nanogel as ophthalmic delivery system of curcumin: development, characterization, in vitro permeation and in vivo pharmacokinetic studies. Pharmaceutical development and technology. 2016;21(5):576-82. https://doi.org/10.3109/10837450.2015.1026607 PMid:26024239

60. Ameeduzzafar, Ali J, Fazil M, Qumbar M, Khan N, Ali A. Colloidal drug delivery system: amplify the ocular delivery. Drug delivery. 2016;23(3):700-16. https://doi.org/10.3109/10717544.2014.923065 PMid:24892625

61. Pal P, Sambhakar S, Paliwal S. Revolutionizing Ophthalmic Care: A Review of Ocular Hydrogels from Pathologies to Therapeutic Applications. Current Eye Research. 2024:1-17. https://doi.org/10.1080/02713683.2024.2396385 PMid:39261982

62. Pandey M, Choudhury H, binti Abd Aziz A, Bhattamisra SK, Gorain B, Su JST, et al. Potential of Stimuli-Responsive In Situ Gel System for Sustained Ocular Drug Delivery: Recent Progress and Contemporary Research. Polymers. 2021;13(8):1340. https://doi.org/10.3390/polym13081340 PMid:33923900 PMCid:PMC8074213

63. Liu H, Jian R, Chen H, Tian X, Sun C, Zhu J, et al. Application of biodegradable and biocompatible nanocomposites in electronics: current status and future directions. Nanomaterials. 2019;9(7):950. https://doi.org/10.3390/nano9070950 PMid:31261962 PMCid:PMC6669760

64. Çağdaş M, Sezer AD, Bucak S. Liposomes as potential drug carrier systems for drug delivery. Application of nanotechnology in drug delivery. 2014;1:1-50. https://doi.org/10.5772/58459

65. Ana Rd, Fonseca J, Karczewski J, Silva AM, Zielińska A, Souto EB. Lipid-based nanoparticulate systems for the ocular delivery of bioactives with anti-inflammatory properties. International Journal of Molecular Sciences. 2022;23(20):12102. https://doi.org/10.3390/ijms232012102 PMid:36292951 PMCid:PMC9603520

66. Silva HD, Cerqueira MA, Vicente AA. Influence of surfactant and processing conditions in the stability of oil-in-water nanoemulsions. Journal of Food Engineering. 2015;167:89-98. https://doi.org/10.1016/j.jfoodeng.2015.07.037

67. Dukovski BJ, Juretić M, Bračko D, Randjelović D, Savić S, Moral MC, et al. Functional ibuprofen-loaded cationic nanoemulsion: Development and optimization for dry eye disease treatment. International Journal of Pharmaceutics. 2020;576:118979. https://doi.org/10.1016/j.ijpharm.2019.118979 PMid:31870964

68. Lopes CM, Bettencourt C, Rossi A, Buttini F, Barata P. Overview on gastroretentive drug delivery systems for improving drug bioavailability. International journal of pharmaceutics. 2016;510(1):144-58. https://doi.org/10.1016/j.ijpharm.2016.05.016 PMid:27173823

69. Fathi-Karkan S, Ramsheh NA, Arkaban H, Narooie-Noori F, Sargazi S, Mirinejad S, et al. Nanosuspensions in ophthalmology: Overcoming challenges and enhancing drug delivery for eye diseases. International Journal of Pharmaceutics. 2024;658:124226. https://doi.org/10.1016/j.ijpharm.2024.124226 PMid:38744414

70. Tarannum N, Suhani, Kumar D. Synthesis, characterization and applications of copolymer of β-cyclodextrin: a review. Journal of Polymer Research. 2020;27:1-30. https://doi.org/10.1007/s10965-020-02058-9

71. Asyikin binti Abdul Aziz Z, Ahmad A, Hamidah Mohd-Setapar S, Hassan H, Lokhat D, Amjad Kamal M, et al. Recent advances in drug delivery of polymeric nano-micelles. Current drug metabolism. 2017;18(1):16-29. https://doi.org/10.2174/1389200217666160921143616 PMid:27654898

72. Nayak K, Misra M. A review on recent drug delivery systems for posterior segment of eye. Biomedicine & pharmacotherapy. 2018;107:1564-82. https://doi.org/10.1016/j.biopha.2018.08.138 PMid:30257375

73. Seyfoddin A, Shaw J, Al-Kassas R. Solid lipid nanoparticles for ocular drug delivery. Drug delivery. 2010;17(7):467-89. https://doi.org/10.3109/10717544.2010.483257 PMid:20491540

74. Kumar S, Randhawa JK. High melting lipid based approach for drug delivery: Solid lipid nanoparticles. Materials Science and Engineering: C. 2013;33(4):1842-52. https://doi.org/10.1016/j.msec.2013.01.037 PMid:23498204

75. Gordillo-Galeano A, Mora-Huertas CE. Solid lipid nanoparticles and nanostructured lipid carriers: A review emphasizing on particle structure and drug release. European Journal of Pharmaceutics and Biopharmaceutics. 2018;133:285-308. https://doi.org/10.1016/j.ejpb.2018.10.017 PMid:30463794

76. Liu P. Nanocrystal formulation for poorly soluble drugs. Dissertationes bioscientiarum molecularium Universitatis Helsingiensis in Viikki. 2013:62.

77. Pardhi VP, Verma T, Flora S, Chandasana H, Shukla R. Nanocrystals: an overview of fabrication, characterization and therapeutic applications in drug delivery. Current pharmaceutical design. 2018;24(43):5129-46. https://doi.org/10.2174/1381612825666190215121148 PMid:30767737

78. Lu A. Amphiphilic and thermoresponsive block copolymers based on hydroxypropyl methyl cellulose as nano-carrier of hydrophobic drugs: Université Montpellier; 2020.

79. Arpicco S, Battaglia L, Brusa P, Cavalli R, Chirio D, Dosio F, et al. Recent studies on the delivery of hydrophilic drugs in nanoparticulate systems. Journal of Drug Delivery Science and Technology. 2016;32:298-312. https://doi.org/10.1016/j.jddst.2015.09.004

80. Garg G, Saraf S, Saraf S. Cubosomes: an overview. Biological and Pharmaceutical Bulletin. 2007;30(2):350-3. https://doi.org/10.1248/bpb.30.350 PMid:17268078

81. Zembala J, Forma A, Zembala R, Januszewski J, Zembala P, Adamowicz D, et al. Technological Advances in a Therapy of Primary Open-Angle Glaucoma: Insights into Current Nanotechnologies. Journal of Clinical Medicine. 2023;12(18):5798. https://doi.org/10.3390/jcm12185798 PMid:37762739 PMCid:PMC10531576

82. Abdelbary AA, Abd-Elsalam WH, Al-Mahallawi AM. Fabrication of novel ultradeformable bilosomes for enhanced ocular delivery of terconazole: In vitro characterization, ex vivo permeation and in vivo safety assessment. Int J Pharm. 2016;513(1-2):688-96. https://doi.org/10.1016/j.ijpharm.2016.10.006 PMid:27717916

83. Lim LT, Ah-Kee EY, Collins CE. Common eye drops and their implications for pH measurements in the management of chemical eye injuries. Int J Ophthalmol. 2014;7(6):1067-8. https://doi.org/10.4137/OED.S16031 PMid:25002817 PMCid:PMC4076205

84. Gawin-Mikołajewicz A, Nartowski KP, Dyba AJ, Gołkowska AM, Malec K, Karolewicz Be. Ophthalmic nanoemulsions: From composition to technological processes and quality control. Molecular pharmaceutics. 2021;18(10):3719-40. https://doi.org/10.1021/acs.molpharmaceut.1c00650 PMid:34533317 PMCid:PMC8493553

85. Hirata H, Mizerska K, Dallacasagrande V, Rosenblatt MI. Estimating the Osmolarities of Tears During Evaporation Through the "Eyes" of the Corneal Nerves. Invest Ophthalmol Vis Sci. 2017;58(1):168-78. https://doi.org/10.1167/iovs.16-20501 PMid:28114576 PMCid:PMC5256685

86. Cassano R, Di Gioia ML, Trombino S. Gel-based materials for ophthalmic drug delivery. Gels. 2021;7(3):130. https://doi.org/10.3390/gels7030130 PMid:34563016 PMCid:PMC8482217

87. Patil S, Kadam A, Bandgar S, Patil S. Formulation and evaluation of an in situ gel for ocular drug delivery of anticonjunctival drug. Cellulose Chem Technol. 2015;49(1):35-40.

88. Patlolla V, Holbrook W, Gizurarson S, Kristmundsdottir P. Evaluation of in vitro mucoadhesiveness and texture profile analysis of doxycycline in situ hydrogels. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2020;75(1):7-12.

89. Askarkar SS, Gupta KR. Design and Evaluation of Ophthalmic Delivery of Bepotastine Besilate From Eye Drop. Pharmaceutical Methods. 2016;7(2). https://doi.org/10.5530/phm.2016.7.16

90. Bose A, Majumdar S, Halder A. Development and statistical optimization of timolol maleate encapsulated liposome using 32 full factorial design. Proceedings of the Indian National Science Academy. 2025:1-15. https://doi.org/10.1007/s43538-025-00387-1

91. Pavčnik L, Prunk M, Trdan Lušin T, Roškar R. Accelerated Predictive Stability Testing: Accelerating Registration Phase and Application of Reduced Designs for Shelf-Life Determination of Parenteral Drug Product. Pharmaceutics. 2025;17(2):160. https://doi.org/10.3390/pharmaceutics17020160 PMid:40006527 PMCid:PMC11858995

92. Slavkova M, Voycheva C, Popova T, Tzankov B, Tzankova D, Spassova I, et al. Ophthalmic In Situ Nanocomposite Gel for Delivery of a Hydrophobic Antioxidant. Gels. 2025;11(2):105. https://doi.org/10.3390/gels11020105 PMid:39996648 PMCid:PMC11854355

93. Patel N, Desai A, Vyas B, Shah P, Shubhada M, Milind U, et al. Integration of Synchronizing In Silico, In Vitro, and In Vivo Strategies for the Development of Antipsoriatic Apremilast-loaded Nanostructured Lipid Carrier Embedded in Hydrogel. AAPS PharmSciTech. 2025;26(5):115. https://doi.org/10.1208/s12249-025-03103-w PMid:40281236

94. Singh AK, Upadhyay PK, Kumar M. Formulation Development and Permeation Studies of Vancomycin Hydrochloride-Loaded Nanostructured Lipid Carrier Incorporated Thermoresponsive In-Situ Gel: A Box-Behnken Design Implemented Approach for Ocular Delivery in Endophthalmitis. Recent Advances in Drug Delivery and Formulation. 2025.

95. Alves dos Santos PN, Braga Andrade Y, Moraes Santana AA, Cordeiro Cardoso J, dos Santos Polidoro A, Loreiro dos Santos A, et al. Characterization of volatile compounds in Eugenia uniflora L. essential oil by GC× GC/TOFMS: exploring its antioxidant potential and in vitro ocular irritation assessment. Journal of Essential Oil Research. 2025;37(1):56-64. https://doi.org/10.1080/10412905.2024.2447713

96. Tan EYS. Biofabrication of choroid-retina tissue construct for modelling of age-related macular degeneration disease 2019.

97. Soliman KA, Ullah K, Shah A, Jones DS, Singh TR. Poloxamer-based in situ gelling thermoresponsive systems for ocular drug delivery applications. Drug Discovery Today. 2019;24(8):1575-86. https://doi.org/10.1016/j.drudis.2019.05.036 PMid:31175956

98. Iohara D, Okubo M, Anraku M, Uramatsu S, Shimamoto T, Uekama K, et al. Hydrophobically modified polymer/α-cyclodextrin thermoresponsive hydrogels for use in ocular drug delivery.

Molecular pharmaceutics. 2017;14(8):2740-8. https://doi.org/10.1021/acs.molpharmaceut.7b00291 PMid:28661690

99. Chandavarkar N, Jindal KC, Malayandi R. In-situ gel forming solution for ocular drug delivery. WO2011018800. 2011.

100. Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, et al. Research progress of in-situ gelling ophthalmic drug delivery system. Asian journal of pharmaceutical sciences. 2019;14(1):1-15. https://doi.org/10.1016/j.ajps.2018.04.008 PMid:32104434 PMCid:PMC7032175

101. Li H, Su X, Cheng H, Zhao F. Thermoplastic and Reprocessable Polyureas Synthesized from CO2-Based Oligourea. ACS Applied Polymer Materials. 2025.

102. Kesavan K, Mohan P, Gautam N, Sheffield VC. Topical Ocular Delivery of Nanocarriers: A Feasible Choice for Glaucoma Management. Current pharmaceutical design. 2020;26(42):5518-32. https://doi.org/10.2174/1381612826666200916145609 PMid:32938345

103. Koutsoviti M, Siamidi A, Pavlou P, Vlachou M. Recent advances in the excipients used for modified ocular drug delivery. Materials. 2021;14(15):4290. https://doi.org/10.3390/ma14154290 PMid:34361483 PMCid:PMC8347600

104. Das B, Chattopadhyay D, Rana D. The gamut of perspectives, challenges, and recent trends for in situ hydrogels: A smart ophthalmic drug delivery vehicle. Biomaterials Science. 2020;8(17):4665-91. https://doi.org/10.1039/D0BM00532K PMid:32760957

105. Ahmed T, Islam MN, Monalisa R, Ehsan F, Huang S-W. Polysaccharides polymers for glaucoma treatment-a review. European Journal of Ophthalmology. 2024;34(2):338-56. https://doi.org/10.1177/11206721231178057 PMid:37231538

106. Tsung T-H, Tsai Y-C, Lee H-P, Chen Y-H, Lu D-W. Biodegradable polymer-based drug-delivery systems for ocular diseases. International Journal of Molecular Sciences. 2023;24(16):12976. https://doi.org/10.3390/ijms241612976 PMid:37629157 PMCid:PMC10455181

107. Zamboulis A, Nanaki S, Michailidou G, Koumentakou I, Lazaridou M, Ainali NM, et al. Chitosan and its derivatives for ocular delivery formulations: Recent advances and developments. Polymers. 2020;12(7):1519. https://doi.org/10.3390/polym12071519 PMid:32650536 PMCid:PMC7407599