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Advancing Ocular Drug Delivery: Harnessing Nanogels to Overcome Limitations and Enhance Therapeutic Efficacy

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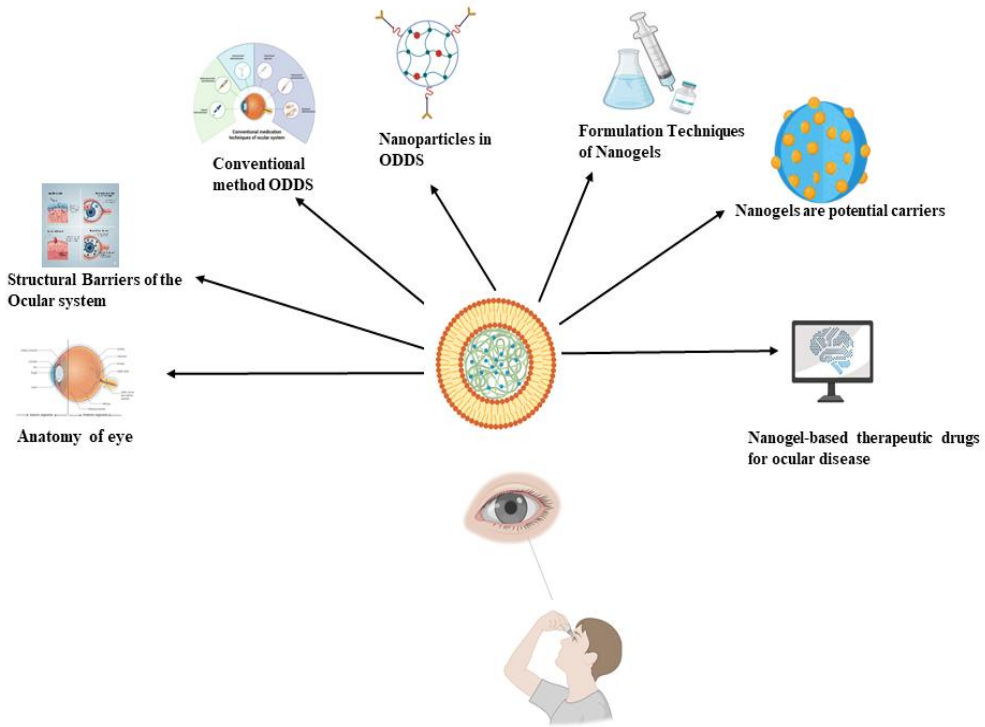
Graphical Abstract



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ABSTRACT

Background: The delivery of therapies for ocular diseases has a broader range of medications, but the administration of drugs is often limited by the anatomical and physiological barriers. This review aims to critically evaluate the translational potential of nanogel-based ocular drug delivery systems (ODD), with a focus on addressing clinical applicability, long-term safety, and scalability while providing a comparative perspective against existing ocular drug delivery systems. In this review, we collected data through a search of peer-reviewed articles in the PubMed database released between 2020 and 2025. Here, we analyzed the common barriers that affect the ocular drug delivery system, conventional methodologies, nanogel drug delivery methods, formulation techniques, and therapeutic methods of nanogel. We have observed that the ODD nanogels have an increased penetration rate, superior precorneal retention, and controlled drug delivery of anterior and posterior segment ailments. Other modern methods, such as stimuli-responsive formulations, hybrid nanogel nanoparticle assemblies, and bioadhesive surface modification, have demonstrated potential in enhancing therapeutic targeting and stability. Nevertheless, issues with long-term safety validation, batch-to-batch reproducibility, and compliance with regulatory standards remain. The effectiveness, safety, and clinical relevance of nanogel-based ocular therapeutics have high potential in changing the face of ocular therapeutics.

1. Introduction

The human ocular system features a complex anatomical structure and physiological barriers that limit the delivery and penetration of drugs. Some common ocular maladies that affect the anterior segment of the eye include dry eye syndrome, glaucoma, allergic conjunctivitis, anterior uveitis, and cataracts. Likewise, the posterior part of the eye develops age-related degeneration of the macula, or amyloid degeneration macular degeneration (AMD), diabetic retinopathy macular edema (DME), proliferative vitreoretinopathy (PVR), posterior uveitis, and cytomegalovirus (CMV) (1). The conventional ophthalmic system of drug delivery to the eye is commonly done with the traditional forms of dosage that include solutions (62.4%), suspensions (8.7%), and ointments (17.4%), among which approximately 90 percent of commercial ophthalmic preparations are done. Topical medication of the eye in the form of gel or drops

contributes 90% of the ocular drug delivery system, as it can be easily applied by patients, but it exhibits poor ocular bioavailability (<5%) because of the lacrimal secretions that contribute to low retention times and reduced permeability across the corneal epithelium (2). The normal eye, with a minimum of 709 µL of tears per minute, is associated with a turnover rate of 0.522 µL/min. Moreover, the topical absorption of the drug is influenced by the blood flow in the conjunctiva. A combination of all the barriers leads to a loss of the drug of approximately 95 percent when applied topically. The remaining part of the drug is exposed to the corneal epithelial barrier (3,4).

Recent advancements in ODD systems have developed a new solution integrating nanotechnology with ocular drug delivery. Nanoparticles are sized between 1 and 100 nanometers, a size that is significantly smaller than that of the cells of the ocular barriers. Due to their size, nanoparticles have the potential to get into the target intrinsic areas of the eye where the drugs can be absorbed (5). Such drug delivery systems tend to show enhanced pharmacokinetic characteristics and can be personalized to release the therapeutic agent in a controlled way, raising safety and effectiveness. Indicatively, nanoparticles can be incorporated into the hydrogel matrix to attain a greater retention time, better resistance to initial degradation, and controlled release of the therapeutic agent, thereby overcoming several of the difficulties that ocular drug delivery implies (6–8). Hydrogel-based systems are one of the examples of the development of such a direction. Advancements in the use of effective ocular drug delivery systems will require a detailed view of the ocular barriers and influencing factors on drug permeation. In order to enhance the contact with biological barriers, researchers have studied various methods of controlling the physicochemical characteristics of nanoparticles, such as surface charge, particle size, and shape, which can determine the efficacy of drug delivery (9–11). The use of certain ligands capable of binding receptors on the target cells or tissues has also proven beneficial in actively targeting drug delivery systems to the preferred site of action (12,13). To enhance these barriers, strategies that are aimed at increasing permeability and retention through active targeting of certain sites, surface charge regulation, and physical and chemical modification of nanocarriers are required. Targeting molecules can be proteins or aptamers that identify targets and can be used in precise and sensitive delivery of the drug, with

promising research results (14,15). The current comprehensive literature review aims to critically evaluate the translational potential of nanogel-based ocular drug delivery systems, with a focus on addressing clinical applicability, long-term safety, scalability, patient compliance, and regulatory challenges, while providing a comparative perspective against existing ocular drug delivery systems.

2. Anatomical structure of the ocular system

The human eye can be broadly segregated into two parts: the anterior (front of the eye) and the posterior (in the eye) parts of the eye. The anterior part of the eye includes the cornea, conjunctiva, iris, ciliary body, crystalline lens, and aqueous humor, while the posterior part includes the sclera, choroid, retina, and vitreous (Figure 1) (16).

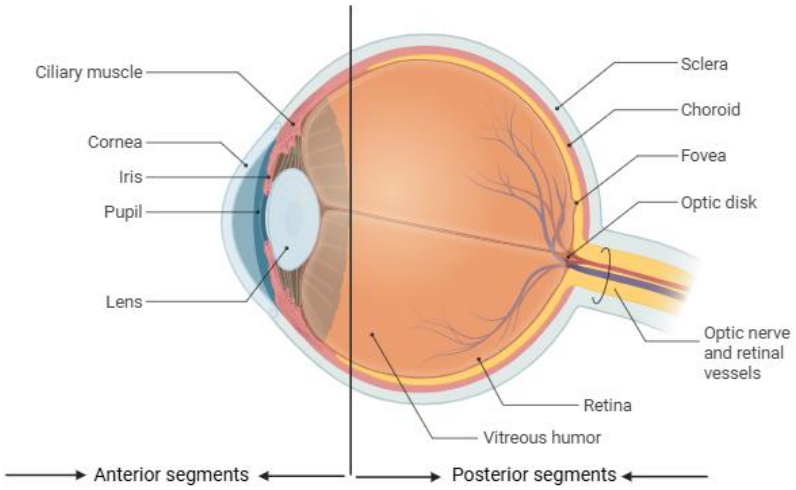


Figure 1: Anatomy of the Eye

Scholars classify the cornea physiologically into five layers: the epithelium, Bowman's membrane, stroma, Descemet's membrane, and inner endothelium (17).

The conjunctiva is a thin, translucent, permeable, vascularized mucous membrane of the first third of the eyeball, more permeable than the cornea and with a higher absorption capacity of the drug, with 22 times the surface (18). Since the conjunctiva has capillaries in the conjunctiva and conjunctival lymphatics, absorption of drugs is usually futile in the conjunctiva. The large volumes of drug waste in the systemic circulation lowering the bioavailability of the ocular drugs, and may induce systemic adverse reactions. A

normal tear volume is 7 µL, but the conjunctival sac can temporarily accommodate up to about 30 µL of tear fluid. The tear fluid turnover is high and reduces the retention time of the ocular drug (19).

The retina is a glassy, clear sense organ in the innermost part of the human eye, made up of various layers of membranes with an average of 249 µm and complex functions of photoconversion and transmission (20). Human visualization of clear images relies on the lens of the anterior part of the eye and the cornea of the eye to concentrate the light of any object on the retina of the eye at the back part. The transparency of the lens is lost, which causes destruction of vision (21–23).

3. Structural Barriers of the Ocular System

The physical and chemical nature of drugs entering the cornea is defined by the hydrophobicity and hydrophilicity of the sandwich structure of the cornea, which necessitates that the large distribution coefficient of the drugs be in both the water phase and the oil phase. While applying, the drug can be influenced by various dynamic or static hurdles found in the tissues, including the tear film barrier, cornea barrier, vitreal barrier, conjunctiva barrier, blood-aqueous barrier, and blood-retina barrier (BRB) (24–26). Figure 2 illustrates the structural barrier of the ODD system.

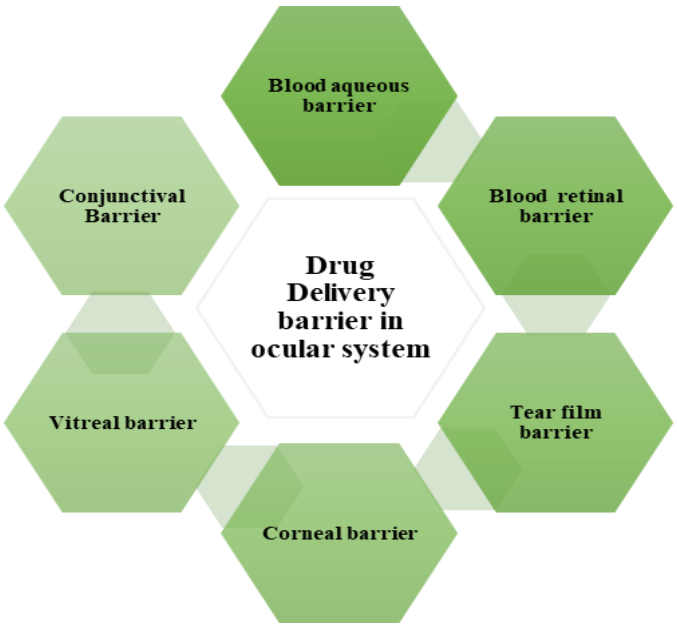


Figure 2: Structural barriers of the eye

3.1. Tear Film Barrier

The primary barrier to topical administration of drugs is the tear film. Precorneal volume is low, and the maximum amount of eye drops that could be held in the conjunctival sac is about 30 µL. Topical administration of eye drops (25-50 µL) showed that only approximately 10 µL of the drug would be left after the blink reflex and nasolacrimal duct drainage (27). The tear film is comprised of an external lipid layer, a mid-aqueous layer, and an inner mucin layer. Hydrophilic and hydrophobic drugs were limited by the lipid and aqueous layers, respectively. The inner tear layer has a negatively charged mucin layer that prevents the entry of negatively charged drugs or carriers into the cornea (28).

3.2. Corneal Barrier

The secondary barrier that prevents the penetration of exogenous substances into the eye is the cornea. It is composed of five layers of collagenous fibers, which include the epithelium, Bowman's membrane, stroma, Descemet membrane, and endothelium. The epithelium, stroma, and endothelium are the layers that create significant barriers against drug penetration. Six to eight layers of cells compose the surface of the corneal epithelium with an overall thickness of about 40-50 mm. As the epithelium cell matures, it becomes flattened and later develops tight intercellular junctions, permitting the passage of hydrophilic drugs (29). A layer of hydrophilic gel next to the corneal epithelium is about 450-500 µm thick, which is 90% of the corneal thickness, and which poses serious advantages to lipophilic drugs with regard to solubility and partition coefficients (30). Similarly, there are tight junctions on the endothelium. The endothelium is less impermeable than the epithelium and less resistant to paracellular passage of drugs due to its thinness in cells (13 µm). The particular sandwich arrangement of corneal tissue renders it an exclusive barrier to the vast majority of lipophilic and hydrophilic drugs (31).

3.3. Conjunctival Barrier

The conjunctiva is a thin, translucent, blood-filled mucous membrane that can be split into three parts, including the bulbar conjunctiva, conjunctival vault, and lid conjunctiva. The conjunctiva, in contrast to the cornea, is regarded as a significant pathway of noncorneal drug delivery (e.g., macromolecular nanoparticles) due to its high vascularity, cupping cells, and transdifferentiation potential (32). The gap between the epithelial cells of the conjunctiva is larger than that of the corneal

epithelial cells, and thus, hydrophilic macromolecules are more likely to penetrate the conjunctiva rather than the cornea. Because of the presence of conjunctival capillaries and lymph, however, ocular administration of drugs is likely to result in a large loss of the circulation of the body, thus decreasing the total ocular availability (17).

3.4. Blood-aqueous barrier

The epithelial tissue of endothelial cells and the non-pigmented ciliary body of the iris vasculature were considered as the blood-aqueous barrier of the eye, which prevents the non-specific entry of various solutes in the intraocular environment (33).

3.5. Blood-retinal barrier

The blood-retinal barrier (BRB) is the most important barrier in the posterior ocular region. The external region of the BRB is made of close junctions between retinal pigment epithelial cells, while the internal region is made of tight junctions between retinal capillary endothelial cells. Thus BRB framework prevents the entry of substances into the retina, which also limits the penetration of medication molecules' ability to enter the intraocular region (34).

4. Conventional medication techniques for the ODD system

The topical delivery route maintains its position as the leading method for drug administration through the eyes because it offers convenient administration and patient adherence. The therapeutic benefits of topical delivery face multiple primary restrictions that reduce drug effectiveness. At present, we have identified more than 500 ocular diseases. Some of them include conjunctivitis, cataracts, glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, endophthalmitis, and ocular tumors (35). The prevalence graph of these conditions grows rapidly due to the long-term exposure of the eye and aging conditions (36). This results in the immediate development of effective medication for the ODD system. Some conventional medication techniques for ODD are shown in Figure 3. The image is created in https://BioRender.com.

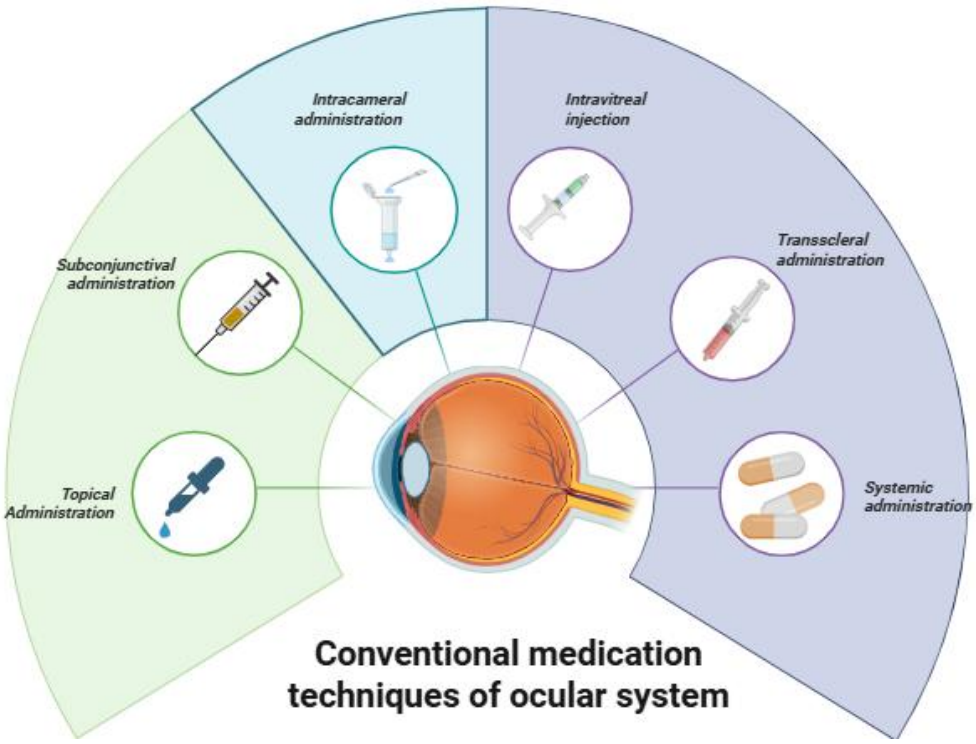


Figure 3: Conventional medication techniques for ODD

4.1. Topical Administration

The most common and widely used medication for the ocular disease is topical administration. Compared to the systemic method, 90 percent of people prefer the topical medication, as it is non-invasive, easy to apply, and has minimal adverse events compared to other systemic techniques (37). However, the ocular barrier, such as the tear film barrier, corneal barrier, and anatomical structure, limits the bioavailability of the drug delivery system. To overcome this limitation, we should improve two strategies: improve the permeability of the cornea and increase the retention time of the pre-corneal drug (38).

4.2. Subconjunctival administration

This is a minimally invasive and effective technique compared to topical administration. Here, the drug is delivered to the anterior or posterior chamber of the eye. This method overcomes the blood-aqueous and corneal barriers. It avoids the potential adverse events and prevents the initial breakdown of some systemic medications. However, the drug loss occurs

in subconjunctival mode due to the drainage of blood and lymphatic fluids through the conjunctiva (39).

4.3. Transscleral administration

This is another minimally invasive method; here, the molecules of size up to 70 kDa can penetrate to the sclera, and a 1 kDa molecule can cross the cornea. But the bioavailability of this process is lower than direct intravitreal ROA due to the dynamic barrier (40).

4.4. Intracameral administration

This is a minimally invasive method where the drug is injected into the anterior chamber of the eye. This method prevents the limitation of subconjunctival administration by preventing the cornea, conjunctiva, and blood-aqueous barriers. This technique is widely used in prophylactic procedures of eye surgeries as anesthetics and antibiotic drugs.

However, this method cannot deliver the drug to the posterior region. Also, the drug in the anterior region should be prepared with appropriate concentration and doses, without preservation. If the process is not done correctly, it may cause endothelial corneal toxicity and toxic anterior syndrome (41).

4.5. Intravitreal injection

Intravitreal injection is used to treat the posterior region of the eye. But frequent injection of the drug is required to achieve a good effect. This results in the eyeball infection, elevated IOP, and other retinal problems. To overcome the effects, researchers developed nanoparticle-based implants, hydrogels, and other minimally invasive techniques that are under the preclinical development stage (42).

4.6. Systemic administration

This method includes oral dose-based medication, used as preferred antibodies to treat conditions such as uveitis and endophthalmitis. Frequent administration of the drug is required to achieve the desired level of therapeutic effect. This may cause systemic adverse events in the patients. Hence, it's not an ideal method for ocular treatment (43).

Multiple conventional techniques, such as corneal prodrugs, mucus osmotic particles, enhancers, collagen corneal shields, and therapeutic contact lenses, were developed in the ocular drug delivery system, yet it has several limitations. In the current era, nanoparticle-based ODD systems have opened up a new perception in the ocular therapeutic system in liquid, gel, and semi-solid formulations of drugs(44).

5. Nanoparticles in Ocular Drug Delivery Systems

5.1. Colloidal nanocarriers

To penetrate the drug molecule in the eye, micelles, liposomes, dendrimers, and dendrimers are used as the colloidal nanocarriers. The drug retention time was increased by mucus-penetrating particles that make contact with the corneal epithelium. Liposome-based mucus-penetrating particles, which a colloidal nanovehicles developed by surrounding an internal aqueous core with a typical size from 10 nm to several micrometers with lipid bilayers (45). By transcellular mechanism, the lipophilic drugs easily penetrate into the lipophilic cornea (46).

5.2. Liposomes

Liposomes, which are coated by mucoadhesive chitosan, allow the medicament to pass through tight junctions and increase the precorneal retention time, making the penetration of topical administration of hydrophilic drugs more feasible. The main drawbacks are decreased bioavailability, stability issues on the mucin surface (the half-life was short due to the tear turnover), and the solubility of drugs is also very poor (47).

5.3. Nanomicelles

Nanomicelles are the colloidal structures composed of amphiphilic molecules/monomers, which can self-assemble in an aqueous solution. They consist of two main components: a hydrophobic inner/core, which stores and interacts with hydrophobic drugs/agents, and a hydrophilic tail that is lengthy and aids the complex in enclosing the aqueous phase. The peculiar arrangement of micelles prevents the direct contact of topically applied hydrophobic pharmaceuticals at the hydrophilic part of the cornea and stroma (48).

5.4. Hydrogel-based therapeutic contact lenses

Hydrogels used in Therapeutic contact lenses provide controlled-release drugs for an extended time with minimal toxicity and maximum therapeutic window. Due to the hydrophilic polymer chains present in hydrogel, it provides a 3d structure and keeps the drug insoluble (49). Bimatoprost (50), latanoprost (51), tafluprost (52), and travoprost (53) appear to have very comparable efficacy regarding IOP reduction in patients with primary open-angle glaucoma.

Microsphere eye drops delivering brimonidine for glaucoma maintained the

intraocular pressure in an in vivo model; it mentioned the efficacy of treatment magnified with higher baseline pressure (54). The main challenges for using hydrogel-based therapeutic contact lenses are toxicity to the cornea, infection risks, and diffusion of oxygen. Table 1 summarizes the advantages of nanogel over conventional delivery systems.

Table 1: *Advantages of nanogel over conventional delivery systems*

Formulation	**Limitation (Conventional)**	**Nanogel Advantage**	**Reference**
Liposomes	Poor stability, leakage, and fusion of drugs	Nanogels have better structural integrity and reduced leakage	(55)
Solid Lipid Nanoparticles	Drug expulsion during long storage due to polymeric transition	Nanogels allow stable encapsulation and better long-term storage	(56)
Polymeric Nanoparticles	Burst release, particle aggregation, and toxicity	Nanogels enable controlled release and better colloidal stability	(57)
Dendrimer	Blurred vision and potential toxicity	Nanogels are more biocompatible and less irritating to ocular tissues	(58)
Stimuli-Responsive Gel	Limited to smaller molecular weight drugs, poor stability, and temperature sensitivity	Nanogels can encapsulate macromolecules and offer responsive release with better stability.	(59)
Inorganic Nanoparticles	Poor stability and bioavailability	Nanogels offer improved solubility and biocompatibility	(60)
Conventional Eye Drops	Rapid drug clearance, low bioavailability, frequent dosing	Nanogels offer mucoadhesiveness, sustained release, and enhanced corneal permeability	(61)
Conventional Gels	Blurred vision, discomfort, and hydrophobic drug delivery limitations	Nanogels are transparent and suitable for hydrophobic and hydrophilic drugs	(62)

6. Formulation Techniques of Ocular Nanogels

6.1. Precipitation polymerization

Precipitation starts, and polymerization takes place in the homogeneous solution. and polymerization begins with the formation of a homogeneous mixture. Crosslinking polymer chains are needed to isolate particles due to the resulting polymers being soluble in the medium but not swellable. When the polymerization reaction increases, the polymer chain's length also increases. The developed phase is separated to produce polymer colloidal particles, and subsequently, Nanogel is formed after the polymer chain reaches a specific length (63). Synthesis of poly(N-isopropylmethacrylamide) (p(NIPMAM)) nanogels in vitro model to determine the effect of stiffness on cross-translocation in an of the blood-brain barrier (BBB) (64). The results showed that the stiffness of a nanogel is important in biological interactions. The softest nanogels (NG1.5 and NG5) seem more suitable for drug applications as they have better transcytosis across the barrier, while the stiffer ones (such as NG14) have increased cellular uptake. These types of nanogels were shown to be effective in overcoming the physiological barriers (Figure 4) (65).

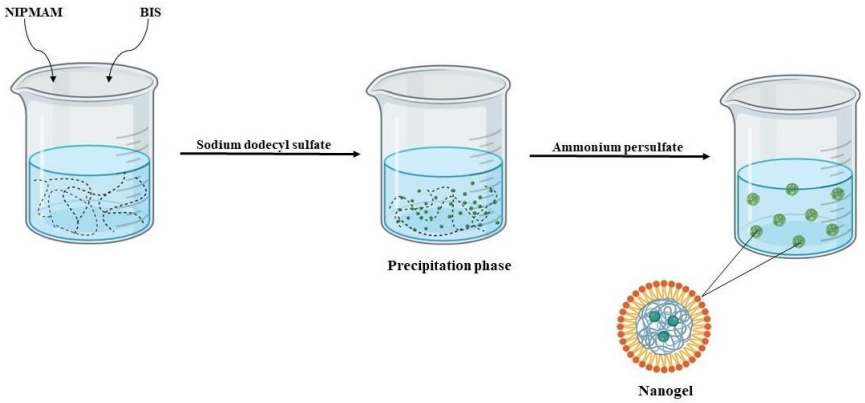


Figure 4: Formulation of Precipitation Polymerization Nanogels

6.2. Inverse emulsion polymerization

The method is based on dispersing the aqueous phase, comprising hydrophilic monomers and carbon nanomaterials, into a continuous oil phase, resulting in the generation of water-in-oil (W/O) droplets stabilized by surfactants. The Initiation of

polymerization occurs within the limits of these droplets and results in the formation of nanogels containing carbon nanomaterials. Significantly, it has full control over the size of the nanogels in addition to enabling efficient incorporation of carbon-based materials that enhance further functionalities for biosensing, bioimaging, and responsive drug delivery applications (66). The synthesis of pH-sensitive poly (L-AGA) (N-acryloyl-L-glutamic acid) nanogels via inverse emulsion polymerization, where dissolving L-AGA and BIS (N, N'-methylene bis(acrylamide)) in a salt solution (0.15 M NaCl) functioning as a dispersed aqueous phase and stabilizes this in an organic phase based on cyclohexane and PGPR (polyglycerol polyricinoleate) surfactant. The synthesized nanogels (between 280 and 370 nm) have high drug-loading capacity qualities, which are quite beneficial in the controlled drug delivery aspect (Figure 5) (67).

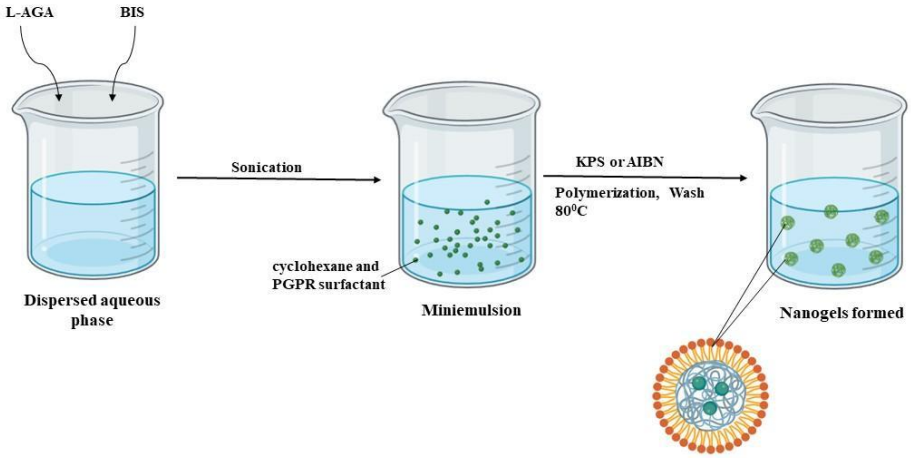


Figure 5: Formulation of Inverse emulsion polymerization nanogels

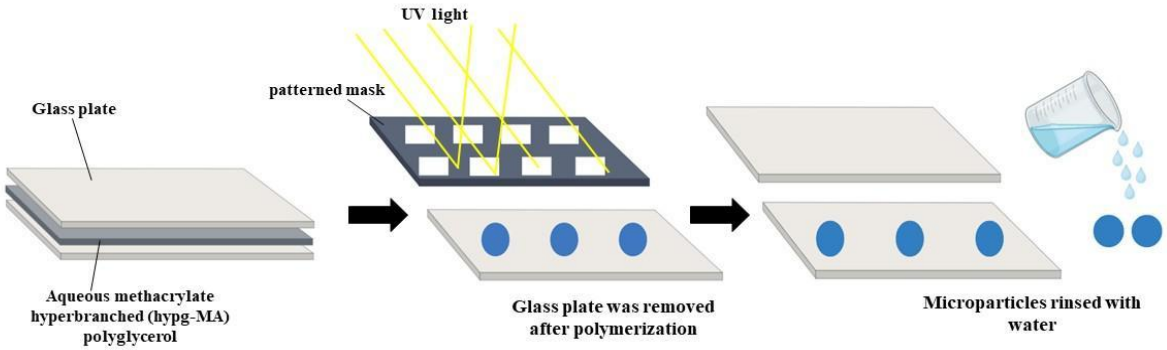
6.3. Microtemplate polymerization

The process of adding monomers along with crosslinkers to microtemplates constitutes microtemplate polymerization. Free radical polymerization starts through an initiating process. The hydrogel nanoparticles emerge from the microtemplate during the final step. The method provides an advantage for generating nanogels of multiple shapes (68). The photolithographic

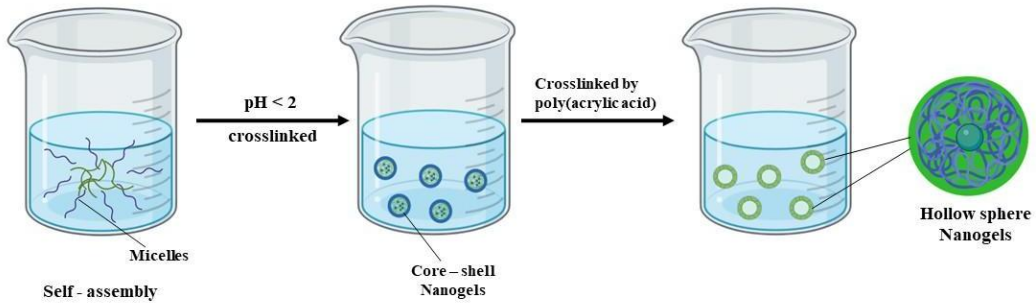
microtemplate polymerization technique is a specific kind of microtemplate polymerization in which a photoinitiator is added along with a monomer and crosslinking agents (Figure 6).

Figure 6: Formulation of microtemplate polymerization nanogels

6.4. Self-assembly and cross-linking



The process by which molecules assemble into thermodynamically stable aggregates through non-covalent interactions is referred to as self-assembly. Molecular self-assembly is mainly caused by van der Waals forces, hydrophobic contacts, electrostatic interactions, and hydrogen



bonding interactions. These interactions may induce water-soluble polymers with particular structures to self-assemble into nanogels. The nanogel's stability can be significantly advanced with the methods of chemical and optical crosslinking. By using the disulfide bonds for crosslinking, the resultant nanogels can respond to the reductive breakdown of certain agents, such as glutathione in cells. pH-dependent nanogels synthesized from hydroxyethyl cellulose-graft-poly(acrylic acid) (HEC-graft-PAA) a self-assembled and crosslinked HEC-graft-PAA nanogels, which offer biomedicine tunable structures and controlled drug release (Figure 7)(69).

Figure 7: Formulation of self-assembly and cross-linking nanogels

6.5. Reverse micellar method

The reverse micellar method employs the water-in-oil dispersion phenomenon, similar to the inverse miniemulsion method. A micellar solution with water droplets dispersed in a continuous oil phase can be obtained thermodynamically stably by using an excessive amount of hydrophilic surfactant. In the size range of about 10-150 nm, the fine nanoparticles within the gel particles exhibit a characteristic. Cross-linking agents prove indispensable for keeping nanoparticles stable, and it is necessary to have the right amount of oil-soluble surfactant to produce thermodynamically stable nanogel particles (70). Reverse micellar was an efficient strategy to comprise self-assembled thermoresponsive nanogels for optimizing drug solubility and permeability, as well as retention time for effective ocular drug delivery (Figure 8).

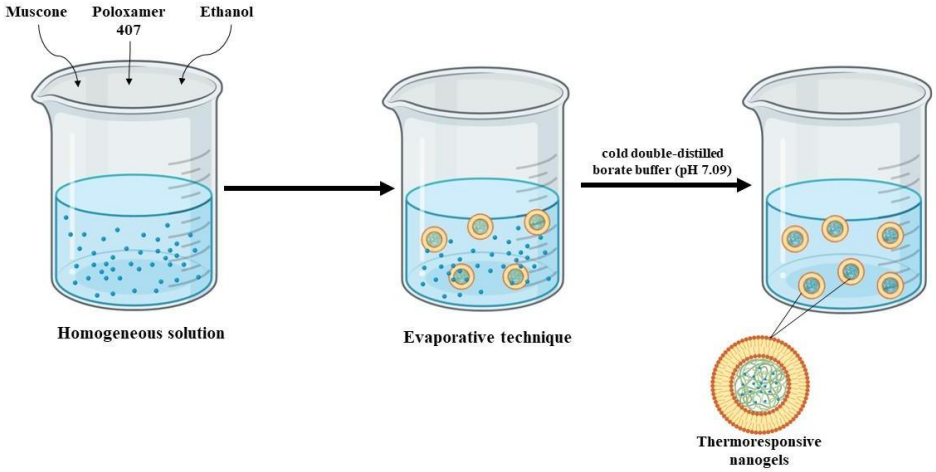


Figure 8: Formulation of reverse micellar method nanogels

7. Nanogels are potential carriers for ocular drug delivery systems

Ocular disorders comprise numerous conditions that affect the entire network of tissues in the eye, starting from the cornea down to the lens and retina and ending with the optic nerve. These health conditions lead to blindness when they receive improper medical treatment. Three primary eye conditions include cataracts, which make the lens appear clouded; glaucoma, which damages the optic nerve in conjunction with increased intraocular pressure; and age-related macular degeneration (AMD), which remains the main cause of central vision loss in older

adults (71). The eye faces multiple significant issues, including uveitis, which affects the uvea; dry eye syndrome, which produces irritation from reduced tear production; retinitis pigmentosa, which results from inherited retinal degeneration; diabetic retinopathy, which develops from diabetic blood vessel damage; and conjunctivitis, which creates inflammation of the conjunctiva between the eyes. Medications applied topically or systemically along with surgical procedures blend with new drug delivery systems such as hydrogels, nanoparticles, nanogels, and ocular inserts for addressing targeted and sustained delivery of drugs to the eyes while overcoming ocular barriers (72). Table 2 explain the Recent advancements in ocular Nanogels.

Table 2: *Recent advancements in ocular Nanogels*

Type of Nanogel	**Drug**	**Polymer**	**Disease**	**Ref**
γ-Cyclodextrin-based Nanogels	Dexamethasone	2-Hydroxypropyl-γ-cyclodextrin (HPγCD)	Ocular inflammation	(73)
Chitin Nanogels	Chitosan/β-glycerophosphate	Chitin	Corneal fungal infections (mycotic keratitis)	(74)
Hyaluronan-Cholesterol Nanogels	Dexamethasone, Piroxicam, Tobramycin, Diclofenac Sodium	Hyaluronan conjugated with cholesterol	Anterior and Posterior Segment Ocular Disorders (Dry Eye, Uveitis, Macular Edema, etc.)	(75)
ROS-stimuli-responsive Nanogel	Dexamethasone	β-Cyclodextrin, Adamantane, Hyaluronic Acid, Thioketal	Corneal Neovascularization (CNV)	(76)
Micelle-Nanogel	Ferulic Acid	Hyaluronan, ε-Polylysine, Poloxamer	Corneal Wound Healing	(77)
Mucoadhesive and Responsive Nanogels	Timolol	Poly(N-isopropyl acrylamide) (pNIPA), Acrylic Acid (AAc)	Glaucoma	(78)

Mucoadhesive Chitosan-Based Nanogel	Acetazolamide (ACZ)	Chitosan crosslinked with Sodium Tripolyphosphate (TPP)	Glaucoma	(79)
Chitosan-Alginate (CS-SA) Nanogel	Timolol Maleate	Chitosan (CS) and Sodium Alginate (SA)	Glaucoma	(80)
Zwitterionic Nanogels	Levofloxacin	Poly(sulfobetaine methacrylate) (PSBMA)	Ocular infections	(81)
Polyelectrolyte Complex (PEC) Nanogels	Nicotinamide Adenine Dinucleotide (NAD^+)	Hyaluronic Acid (HA), Poly(L-lysine) (PLL)	Age-related Ocular Diseases (Glaucoma, Age-related Macular Degeneration)	(82)
Polyvinyl Alcohol (PVA)-based Composite Nanofiber	5-Fluorouracil (5-FU)	Polyvinyl Alcohol (PVA), Fenugreek, Coriander	Post-trabeculectomy Fibrosis in Glaucoma Treatment	(83)
Chitin Nanogels (part of a thermosensitive in situ gel)	Fluconazole	Chitin, Eudragit RS100, Eudragit RL100	Fungal Keratitis and Endophthalmitis	(84)

8. Nanogel-based therapeutic drugs for ocular disease

The intraocular tissues retain less than 5% of the administered medication because most of it gets lost through protective barriers (85). Drugs on the ocular surface remain for a short period, and the cornea exhibits low drug permeability, resulting in reduced bioavailability of medications, particularly those destined for the posterior eye segment. Advanced drug delivery systems became necessary because existing systems fail to maintain drug retention in the eye while also improving drug permeability and delivering medications in controlled amounts.

The utilization of nanogels represents a promising solution to overcome common challenges in conventional topical pharmaceutical delivery through the eyes. Nanoparticle-sized three-dimensional hydrophilic polymeric networks have mucoadhesive qualities that improve drug

maintenance on the ocular surface through their response to both physical stimuli and ion changes (86). Nanogels penetrate biological tissue more efficiently because of their size, while their water content maintains material compatibility with biological structures and prevents tissue irritation. Nanogels function as drug carriers that encapsulate drugs of both hydration-resistant and hydration-friendly natures while controlling their drug release rates to reduce dosage frequency and boost treatment adherence. Their ability to create a depot deposition at application sites permits drugs to stay longer while improving distribution effectiveness, particularly for medicines intended for anterior and posterior ocular regions (87).

Glaucoma develops as an eye disease that manifests through elevated intraocular pressure (IOP). Medical research demonstrates that elevated intraocular pressure and the fluctuations of pressure levels function as key factors in glaucoma development and disease progression (88). The first medical intervention for glaucoma treatment includes eye drops, which are applied topically. Most current eye care procedures function to either reduce Intraocular pressure levels or maintain its stability. Various drugs such as β-blockers, α-agonists, carbonic anhydrase inhibitors, prostaglandin analogs, and cholinergic drugs are commonly used, but their usage is restricted by bioavailability issues (89). The treatment of glaucoma faces two significant challenges from patient adherence alongside medication effectiveness because of the dose requirements for everyday use. Timolol maleate (TM) represents one glaucoma care drug, but medical providers choose other options since its therapeutic benefits are imperfect with daily repeated administration requirements. Systemic side effects pose major risks to patients when using TM as a β-blocker agent (90). Nanocarriers present an alternate drug delivery solution because they allow effective long-term drug release from their ocular encapsulation system. The encapsulation of TM inside nanocarriers, including Nanogels, serves as an approach to extend the therapeutic drug exposure duration in the eye.

Cataracts stand among the main causes of blindness worldwide, while surgery remains the most common treatment approach. Lens epithelial cells create visual problems among numerous patients who undergo surgery through their postoperative proliferation and cellular spread because they evolve into fiber-shaped cells and fibroblast cells (91). Postoperative complication called posterior capsular opacification (PCO) forms in 20–40% of adult cataract patients after surgery but

lacks tested drugs for clinical treatment. Post-cataract surgery use of intraocular lenses implanted into the lens capsule functions as a preventive measure against Nanogels made from nanofibers helps to overcome the Capsular Opacification (CO), which develops following cataract surgery because of Epithelial to mesenchymal transformation (EMT) transitions in lens epithelial cells (LECs). Nanogels made from low molecular weight gelators (LMWGs) which integrated extracellular matrix (ECM)-derived peptides when injected into porcine capsular bags. These peptides IKVAV (isoleucine-lysine-valine-alanine-valine) and YIGSR (tyrosine-isoleucine-glycine-serine-arginine) are both laminin-derived, and RGDS (arginine-glycine-aspartic acid-serine) and PHSRN (proline-histidine-serine-arginine-asparagine) are fibronectin-derived peptides together with DGEA (aspartic acid-glycine-glutamic acid-alanine) is a collagen IV-derived peptide bind integrin-mediated signaling elements to control LEC cellular functions.

The multifactorial condition known as dry eye syndrome (DES), also referred to as dry keratoconjunctivitis, causes complex disorders in the eye. DES causes the breakdown of tear film maintenance alongside tears evaporating faster or slower than needed, because of which eyes become unable to properly lubricate themselves. Due to dry eye syndrome, patients experience eye discomfort and tissue damage, leading to severe vision loss that disables normal human functioning (92). Eye drops containing DES need high dosages and multiple applications per day because their short residence time in the precorneal area leads to less than satisfactory outcomes. After topical application on the eye, PAAc creates a long-lasting lubricating surface that forms directly on the conjunctiva and cornea. The substance exhibits resistance at body temperatures, which causes eye blur and obstructs the blinking motion (93).

Scientists have developed nanogels to address dry eye syndrome (DES), which manifests as an eye condition due to insufficient tear production and excessive tear dryness that leads to surface damage. Nanoscale hydrogel was combined using poly(acrylic acid) (PAAc) and polyvinylpyrrolidone (PVP) through green gamma irradiation into a single-step synthesis to develop biomimetic tear substitutes with low viscosity. Gamma irradiation cross-linked the hydrogels by forming stable nanogels through interpolymer complexation, which occurred through hydrogen bonds and radiation-induced cross-linking.

The nanogels spread quickly on the ocular surface because of their small dimensions and maintained effective contact through their interaction with tear film mucin that delayed drug clearance and cut down the need for frequent eye drops. PAAc-rich nanogels with 20 kGy irradiation doses showed the most potential in improving tear quantity (measured by Schirmer's test) and maintaining tear film stability (measured by tear break-up time, TBUT), as well as preserving corneal epithelial health in albino rabbits with atropine sulfate-induced dry eye pathology. Nanogel formulations containing PVP/AAc ratios at 25/75 mol/mol% and 35/65 mol/mol% took only three days of twice-daily application to restore tear parameters better than the commercial tear gel product Vidisic® needed. The research indicates PAAc/PVP nanogels represent a patient-friendly approach to replace conventional artificial tears for treating DES effectively (94).

Keratitis develops from inflammatory infections together with microorganisms and bacterial entities such as Pseudomonas aeruginosa, Staphylococcus aureus, and Streptococcus pneumoniae that release proteins leading to direct or indirect corneal damage. In situ gels share structural similarities with nanogels because they contain environmentally responsive polymers. It underwent a liquid-to-gel transformation after eye insertion and established a viscoelastic form that steadily delivers medication .

The synthesized nanogels functioned with 10–50 nm particle dimensions and achieved more than 95% success in capturing CIP. The in vitro drug release analysis demonstrated that ciprofloxacin was delivered slowly over five days, while the system first dispensed medication rapidly as a burst and then maintained controlled drug diffusion. The nanoformulated CIP achieved a lower minimum inhibitory concentration value of 4.687 µg/ml against P. aeruginosa compared to 18.78 µg/ml for the conventional CIP solution, thus indicating better antibacterial properties. The use of CIP-loaded nanogels proved more effective than CIP solution at reducing ulcer area in severe keratitis cases when applied to rabbits. Nanogels proved to be safe for use despite their lack of damage to the eyes, which further helped therapeutic success through their ability to sustain drug levels at the infected tissue (95). The study demonstrates that P(NIPAAm-MAA-VP) nanogels present a potential substitute to traditional ocular antibiotic therapies for prolonged localized bacterial keratitis treatment .

9. Limitations and future perspective

The nanogel appears to be a viable approach to the setting of ocular drug administration, conferring potential advantages such as sustained and controlled release of drugs, increased bioavailability, and improved patient compliance. The main challenge in the nanogel-based technology is the formulation process of the drug, which is highly influenced by it complex permeability and bioavailability. We observed that most of the nanogel based techniques are preclinical stage, thus limiting the availability of clinical data. Future advancements in nanogel technology will mainly focus on the formulation of multi-stimuli-responsive nanogels responding to pH, temperature, enzymes, and oxidative stress. Moreover, hybrid nanogels, having liposomes or micelles or any other kind of nanocarrier, may encapsulate and release drugs, which would augment the therapeutic effectiveness. The next vital area of research will be the choice of suitable polymers that will minimize toxicity while having a high payload capacity and, thus, maximizing safety and biocompatibility. The use of nanogels to transport genes and proteins also holds great promise and may pave the way for therapies targeting degenerative and hereditary eye diseases. Depending upon future advances, it may be possible to make greater therapeutic use of nanogels by employing biosensors to monitor real-time drug release and treatment response. However, for commercialization issues, regulatory approval, and long-term safety considerations to be addressed, it is mandatory that extensive in vivo and clinical studies are performed to get clinical acceptance on a wide scale.

10. Conclusion

In this review, we studied the anatomical structure of the eye, structural and functional barriers of ocular disease, conventional ODD technologies, and how nanogel methods help to overcome this method. We analysed that nanogel-based techniques have high efficacy compared to the conventional ocular therapeutic methods, particularly to avoid the drainage of drugs. This controlled release of drug, increased viscoelasticity, and bioavailability nature improved the efficacy of the drug. Their unique properties, such as mucoadhesion, high hydration, and controlled drug release, will help in overcoming the limitations of classical ophthalmic formulations. The effectiveness, safety, and clinical relevance of nanogel-based ocular therapeutics will be vastly enhanced with further

advancements in polymer chemistry and nanotechnology. Nanogels can truly revolutionize the treatment of some ocular diseases with further study and development, eventually improving patient outcomes and quality of life.

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For manuscript preparation, the authors utilized Quillbot Premium and Grammarly to enhance the clarity readability. The authors have also used Biorender for the preparation of images and Chemsketch for the preparation of structures of the molecules. The final version of the manuscript has been properly checked, verified and approved by all the authors.

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