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Ocular Drug Delivery Systems: Barriers, Nanocarrier-Based Approaches, In Situ Gelling Formulations, and Recent Clinical Advances

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Abstract:

Background: Ocular drug delivery remains one of the most challenging problems in pharmaceutical science, constrained by a unique set of anatomical and physiological barriers that limit conventional eye drop bioavailability to less than 5% of the instilled dose. The eye possesses a dual compartment anatomy — anterior and posterior segments — separated by anatomical barriers including the lens, ciliary body, and vitreous humor, each imposing distinct pharmacokinetic challenges for topical, intravitreal, periocular, and systemic drug administration routes. The rising global burden of posterior segment diseases including age-related macular degeneration, diabetic retinopathy, glaucoma, and uveitis, combined with the inadequacy of monthly or bimonthly intravitreal injection regimens for maintaining long-term drug levels in the vitreous, has created an urgent need for advanced drug delivery systems that extend dosing intervals, improve patient compliance, and reduce the risks associated with repeated intraocular injections.

Objective: This review critically examines the anatomical and physiological barriers to ocular drug delivery, the classification and formulation design of ocular drug delivery systems including topical formulations, nanoparticles, liposomes, in situ gelling systems, ocular implants, and contact lens-based delivery, mechanisms of ocular drug absorption, therapeutic applications across anterior and posterior segment diseases, and recent clinical advances through 2023.

Results and Discussion: Nanocarrier-based ophthalmic formulations including polymeric nanoparticles, solid lipid nanoparticles, liposomes, cubosomes, and dendrimers achieve significantly greater corneal drug penetration and precorneal residence time compared to conventional eye drops, with in vivo bioavailability improvements of two- to tenfold documented in animal models. In situ gelling systems — responsive to pH, temperature, or ion concentration — extend the precorneal residence time from minutes to hours by forming a viscous gel depot upon contact with the ocular surface, improving bioavailability without the patient compliance limitations of viscous eye drops. For posterior segment delivery, biodegradable implants and drug-eluting devices have demonstrated sustained intravitreal drug levels for three to thirty-six months, dramatically reducing injection frequency compared to monthly intravitreal injections.

Conclusion: Advanced ocular drug delivery systems represent a scientifically mature field with multiple clinically approved products demonstrating meaningful clinical benefits, including substantial reductions in intravitreal injection frequency and sustained visual acuity improvements. The principal unmet needs

are in truly non-invasive posterior segment drug delivery and in universal patient acceptance of contact lens-based and sustained-release topical delivery systems.

Keywords: *Ocular drug delivery; eye drops; nanoparticles; in situ gel; intravitreal implant; corneal permeation; glaucoma; macular degeneration; diabetic retinopathy; contact lens drug delivery*

1. Introduction

The eye is a complex sensory organ enclosed within a protective anatomical fortress of barriers — the bony orbit, eyelids, lacrimal drainage system, corneal epithelium, blood-aqueous barrier, and blood-retinal barrier — that evolved to protect the delicate retinal photoreceptors and vitreous humor from infectious agents, chemical toxins, and immune cells. These same protective barriers impose severe constraints on drug delivery to ocular tissues, making the eye one of the most pharmacokinetically restrictive organs in the human body for therapeutic drug administration [1,2].

The global burden of ocular disease is substantial and growing. Age-related macular degeneration affects approximately 196 million people worldwide and is the leading cause of legal blindness in developed countries. Diabetic retinopathy affects one-third of diabetic patients — approximately 140 million people globally — and is the most common cause of new-onset blindness in working-age adults. Glaucoma affects 76 million people globally and is the leading cause of irreversible blindness worldwide. These three diseases alone represent an enormous burden of visual disability for which current pharmacological therapy, while effective, is constrained by poor drug bioavailability in target tissues and by the burden of frequent drug administration [3,4].

The inadequacy of conventional eye drops — which deliver less than 5% of the instilled drug dose to intraocular tissues, with the remainder lost to nasolacrimal drainage, systemic absorption, and precorneal clearance — has driven four decades of research into advanced ocular drug delivery systems. These include mucoadhesive systems that extend precorneal residence time, nanocarriers that enhance corneal permeation and protect labile drugs from precorneal enzymatic degradation, in situ gelling systems that form viscous depots on the ocular surface upon instillation, contact lens platforms that deliver drug through prolonged ocular surface contact, and implantable intravitreal devices that sustain therapeutic drug concentrations in the vitreous for months to years [5,6].

The posterior segment of the eye — retina, choroid, vitreous, and optic nerve — presents the greatest drug delivery challenge because topically instilled drugs rarely reach it at therapeutic concentrations due to the anatomical separation imposed by the lens, ciliary body, and vitreous. Monthly or bimonthly intravitreal injection is currently the standard of care for wet age-related macular degeneration and diabetic macular oedema, delivering anti-VEGF biologics directly into the vitreous humor. While clinically effective, this injection regimen imposes a substantial treatment burden, with the injection frequency and associated risks of endophthalmitis, retinal detachment, and vitreous hemorrhage representing major barriers to long-term treatment adherence [7].

This review examines the anatomy and physiology of ocular barriers, the diverse formulation strategies developed for anterior and posterior segment ocular drug delivery, the mechanisms of ocular drug absorption and penetration, and the therapeutic applications of advanced ocular delivery systems in glaucoma, macular degeneration, diabetic retinopathy, dry eye disease, and infectious conditions. A critical analysis addresses the methodological limitations of preclinical ocular pharmacokinetic studies and the translational challenges in converting animal model findings to clinical efficacy.

2. Scientific Background

2.1 Anatomy of the Ocular Drug Delivery Barrier

The eye is anatomically divided into anterior and posterior segments by the lens. The anterior segment contains the cornea, anterior chamber, iris, ciliary body, trabecular meshwork, and lens. The posterior segment contains the vitreous humor, retina, choroid, Bruch's membrane, and optic nerve head. Drug delivery to these compartments faces distinct barrier sets: the precorneal, corneal, and blood-aqueous barriers for anterior segment delivery; and the blood-retinal barrier, vitreous diffusion limitation, and choroidal clearance for posterior segment delivery [8,9].

The cornea is composed of five layers in humans: the epithelium (five to seven cell layers, 50 to 60 micrometers thick), Bowman's layer (a collagenous basement membrane), the stroma (500 micrometers of organized collagen lamellae accounting for 90% of corneal thickness), Descemet's membrane, and the endothelium (a single cell monolayer). The corneal epithelium is the primary permeation barrier for topically applied drugs, forming tight junctions between superficial squamous cells that restrict paracellular

permeation and limit transcellular passage to lipophilic molecules. The aqueous stroma, in contrast, is permeable to hydrophilic molecules, creating a biphasic permeation barrier that ideally suited molecules must negotiate by having both lipophilic (for epithelial penetration) and hydrophilic (for stromal diffusion) characteristics [10].

2.2 Precorneal Drug Loss Mechanisms

Following instillation of a conventional eye drop (typically 30 to 50 microliters), the human conjunctival sac with a normal tear volume of 7 to 10 microliters can accommodate only 20 to 30 microliters before drainage occurs. The excess volume is immediately drained through the nasolacrimal system into the nasal mucosa and nasopharynx, from which systemic absorption can occur. Basal tear turnover of approximately 1 microliter per minute, driven by lacrimal secretion and nasolacrimal drainage, continuously dilutes and removes drug from the precorneal space. Reflex blinking stimulated by eye drop instillation temporarily increases this drainage rate. The combined effects of drainage, dilution, and tear turnover reduce the precorneal contact time of a conventional eye drop to approximately 5 to 10 minutes for a liquid formulation, severely limiting corneal absorption [11,12].

2.3 Blood-Retinal Barrier

The inner and outer blood-retinal barriers (iBRB and oBRB) restrict systemic drug access to the retina. The iBRB is formed by tight junctions between retinal capillary endothelial cells, analogous in structure and function to the blood-brain barrier. The oBRB is formed by tight junctions between retinal pigment epithelial (RPE) cells that separate the fenestrated choriocapillaris from the retinal photoreceptor layer. Together, these barriers exclude systemically administered drugs from the neural retina at therapeutically relevant concentrations, making topical or systemic drug administration routes ineffective for posterior segment therapy of most drug molecules [13].

3. Classification of Ocular Drug Delivery Systems

3.1 Conventional Topical Formulations

Conventional ophthalmic eye drops in aqueous solution remain the most widely used ocular drug delivery form for anterior segment conditions including glaucoma, dry eye, conjunctivitis, and post-operative inflammation. Their advantages of ease of administration, patient familiarity, and low manufacturing cost are offset by their fundamental pharmacokinetic limitations of low bioavailability (typically 1 to 5%), frequent dosing requirements (two to four times daily), and systemic absorption through nasolacrimal drainage that can cause cardiovascular, respiratory, and central nervous system adverse effects with beta-blocker and carbonic anhydrase inhibitor eye drops [14].

3.2 Viscosity-Enhancing and Mucoadhesive Formulations

Viscosity-enhancing agents including hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC), polyvinyl alcohol (PVA), polyethylene glycol, and sodium hyaluronate are incorporated into ophthalmic formulations to extend precorneal residence time by slowing drainage and increasing contact time with the corneal surface. Mucoadhesive polymers including carbopol, chitosan, sodium hyaluronate, and cellulose derivatives bind to mucin glycoproteins on the ocular surface through non-covalent interactions, further retarding precorneal clearance. Hyaluronate-based artificial tears and lubricant eye drops containing CMC are among the most widely prescribed products for dry eye disease, exploiting the viscosity and mucoadhesive properties of these polymers to restore tear film stability [15].

3.3 Nanoparticle-Based Ophthalmic Systems

Polymeric nanoparticles fabricated from PLGA, chitosan, albumin, or zein and sized between 100 and 500 nanometers have been extensively investigated for ophthalmic drug delivery, exploiting their capacity to penetrate the mucus layer of the tear film, adhere to the corneal surface, prolong precorneal drug residence, and protect encapsulated drugs from enzymatic degradation in tear fluid. Nanoparticles in the 100 to 300 nm size range demonstrate the greatest corneal epithelial cell uptake by endocytosis. Surface coating with chitosan provides mucoadhesive and permeation-enhancing properties through electrostatic interaction with anionic corneal surface glycoproteins and transient tight junction opening [16,17].

3.4 Liposomes and Lipid-Based Ophthalmic Carriers

Liposomes offer superior biocompatibility and similarity to biological membranes, enabling encapsulation of both hydrophilic drugs (in the aqueous interior) and lipophilic drugs (in the lipid bilayer) within a single

carrier. Ophthalmic liposomes formulated from phosphatidylcholine, phosphatidylserine, and cholesterol interact favorably with the lipid-rich corneal epithelial membrane, facilitating drug permeation. Cationic liposomes with positive surface charge demonstrate enhanced corneal adhesion through electrostatic interaction with the negatively charged corneal surface glycoproteins. PEGylated stealth liposomes demonstrate prolonged precorneal residence time by reducing complement-mediated and macrophage-mediated clearance from the tear film [18].

3.5 In Situ Gelling Ophthalmic Systems

In situ gelling ophthalmic formulations are liquid at the time of administration, enabling instillation as conventional eye drops, but undergo a sol-gel transition upon contact with the ocular surface in response to physiological triggers including temperature, pH, or ionic concentration. This transition converts the initially low-viscosity formulation into a viscous gel depot on the ocular surface that substantially extends precorneal residence time — from the 5 to 10 minutes of conventional drops to 1 to 4 hours for gelling systems — by resisting nasolacrimal drainage while maintaining comfortable wear [19,20].

3.6 Contact Lens-Based Drug Delivery

Therapeutic contact lenses that release drug to the ocular surface during their wearing period represent an attractive approach to extended ophthalmic drug delivery that leverages an established medical device technology already worn by hundreds of millions of people globally. Drug-loaded contact lenses maintain drug contact with the corneal surface continuously during the wearing period, in contrast to eye drops that are present for only minutes before drainage. Drug loading methods include soaking of commercial lenses in drug solution, molecular imprinting within the lens polymer matrix, vitamin E nanobarrier incorporation, and drug-loaded nanoparticle dispersion within the lens hydrogel [21].

3.7 Intravitreal Implants and Drug-Eluting Devices

Intravitreal implants provide sustained drug release directly within the vitreous humor over periods of months to years, eliminating the need for monthly or bimonthly injections that characterize anti-VEGF therapy for posterior segment diseases. Implants may be biodegradable (releasing drug as the polymer erodes, typically 3 to 12 months) or non-biodegradable (providing sustained release for 1 to 3 years through membrane-controlled diffusion, requiring surgical retrieval after exhaustion). Both types maintain intravitreal drug concentrations within the therapeutic window over their duration, offering dramatically improved patient convenience and compliance compared to injection regimens [22,23].

Table 1: Classification of ocular drug delivery systems by administration route, target tissue, drug residence time, and representative products

System Type	Route	Target Segment	Residence Time	Representative Products / Drugs
Conventional eye drops	Topical	Anterior	5–10 min	Timolol, latanoprost, ciprofloxacin, dexamethasone
Viscosity-enhanced drops	Topical	Anterior	15–30 min	CMC artificial tears, HPMC lubricants, PVA drops
In situ gelling systems	Topical	Anterior / conjunctiva	1–4 hours	Timolol poloxamer gel, pilocarpine gellan gel
Nanoparticles	Topical	Anterior	1–6 hours	PLGA NPs, chitosan NPs, SLNs, nanosuspensions
Liposomes / lipid NPs	Topical / intravitreal	Anterior / posterior	2–12 hours	Cyclosporine liposomes, triamcinolone SLN
Contact lens delivery	Ocular surface	Anterior	8–30 hours	Investigational: timolol, latanoprost, ketorolac lenses

Biodegradable implants	Intravitreal / subconjunctival	Posterior	3–12 months	Ozurdex (dexamethasone), Yutiq (fluocinolone)
Non-biodegradable implants	Intravitreal / subconjunctival	Posterior / anterior	12–36 months	Vitrasert, Iluvien, Port Delivery System

CMC: carboxymethylcellulose; HPMC: hydroxypropyl methylcellulose; PVA: polyvinyl alcohol; PLGA: poly(lactic-co-glycolic acid); SLN: solid lipid nanoparticle; NP: nanoparticle.

4. Formulation Design and Development

4.1 Physicochemical Optimization for Corneal Permeation

The physicochemical properties of ophthalmic drugs and their formulations must be optimized to navigate the biphasic corneal permeation barrier — lipophilic epithelium followed by hydrophilic stroma. Prodrug strategies that increase lipophilicity through esterification to improve epithelial penetration, with subsequent enzymatic hydrolysis in the corneal stroma to regenerate the active drug, are employed for ophthalmic drug delivery of several clinically important molecules. Latanoprost, bimatoprost, and travoprost are prostaglandin ester prodrugs formulated as eye drops that penetrate the corneal epithelium more efficiently than the parent prostaglandin acids owing to their greater lipophilicity, with hydrolysis to the active acid form occurring in the corneal epithelium and aqueous humor [24].

Cyclodextrin complexation improves aqueous solubility of lipophilic ophthalmic drugs while simultaneously enhancing corneal permeation — an apparently paradoxical combination explained by the ability of cyclodextrin to serve as a drug reservoir at the corneal surface, releasing free drug for membrane permeation while maintaining high aqueous concentration at the corneal epithelium surface. Hydroxypropyl-beta-cyclodextrin is included in several commercially available ophthalmic formulations as a solubilizer, most notably in Voltaren Ophtha (diclofenac sodium) and in investigational cyclosporine A ophthalmic formulations [25].

4.2 pH and Osmolarity Considerations

Ophthalmic formulations must be formulated within the pH range of 6.0 to 8.0 to avoid corneal damage from acidic or alkaline formulations, with an optimal pH near the physiological tear fluid pH of 7.4. Formulation pH also influences the ionization state of amphoteric drugs, with only the unionized fraction readily permeable across the lipid-rich corneal epithelial membrane. Tonicity matching to the physiological osmolarity of tear fluid (approximately 300 mOsm/kg) is similarly important to prevent osmotic stress to the corneal endothelium. Hypotonic or hypertonic formulations cause corneal edema or epithelial cell shrinkage that can paradoxically enhance permeation of some drugs through disrupted tight junctions but may cause patient discomfort and reflex tearing that accelerates drug clearance [26].

4.3 In Situ Gel Formulation Design

Successful ophthalmic in situ gel formulation requires balancing three conflicting requirements: the formulation must be sufficiently fluid at ambient temperature to pass through the eye drop bottle nozzle and spread across the ocular surface upon instillation; it must gel rapidly at ocular surface temperature (approximately 34°C, slightly below core body temperature) or upon contact with tear fluid ions; and the resulting gel must be sufficiently viscoelastic to resist nasolacrimal drainage without causing blurred vision or foreign body sensation. Poloxamer 407 in concentrations of 18 to 25% w/v undergoes gelation at approximately 25 to 34°C (tunable by concentration and copolymer composition), gelling on contact with the ocular surface after ambient-temperature instillation. Gellan gum (deacylated) gels upon contact with the calcium and sodium ions in tear fluid at concentrations as low as 0.1 to 0.3% w/v [27,28].

4.4 Nanoparticle Surface Engineering for Ocular Applications

The surface properties of ophthalmic nanocarriers critically determine their interaction with the ocular surface mucus layer and corneal epithelium. Chitosan surface coating provides positive surface charge at physiological pH through protonated amine groups, enabling electrostatic interaction with the negatively charged sialic acid residues of mucin glycoproteins on the ocular surface and corneal epithelial cells, enhancing both mucoadhesion and cellular uptake. Thiolated chitosan, through formation of covalent disulfide bonds with cysteine-rich mucin domains, provides substantially stronger and more durable mucoadhesion than unmodified chitosan, extending corneal contact time and enhancing drug bioavailability [29,30].

5. Preparation Methods

5.1 Preparation of Ophthalmic Nanoparticles

PLGA and chitosan nanoparticles for ophthalmic applications are prepared by emulsification-solvent evaporation or nanoprecipitation methods under aseptic conditions using pharmaceutical-grade polymers and excipients. The preparation involves dissolving polymer and drug in an organic solvent (typically ethyl acetate or acetone), emulsifying with an aqueous surfactant phase, and removing the organic solvent by evaporation under reduced pressure. Particle size must be controlled within 100 to 300 nm for ophthalmic applications, as particles above 400 nm cause ocular discomfort and foreign body sensation. Surface modification with chitosan is achieved by coating preformed nanoparticles with chitosan solution through electrostatic interaction between the negatively charged nanoparticle surface and positively charged chitosan [31].

5.2 Preparation of In Situ Gelling Ophthalmic Formulations

Poloxamer-based in situ gels are prepared by the cold dissolution method: poloxamer powder is dispersed in cold water (2 to 8°C) with gentle stirring to fully hydrate the amphiphilic block copolymer, and drug, preservative, and tonicity-adjusting agents are subsequently added and dissolved. The resulting solution must be sterile-filtered through 0.22 micrometer membranes before aseptic filling into sterile containers. Gellan gum-based systems are prepared similarly, with the deacylated gellan gum dissolved in water at 90°C, cooled, and drug added before sterile filtration. The gelation temperature and gelation onset time at simulated tear fluid must be characterized to confirm in situ gelling behavior under clinically relevant conditions [32].

5.3 Intravitreal Implant Fabrication

Biodegradable PLGA intravitreal implants are prepared by hot-melt extrusion of drug-PLGA blends through a precision die, followed by cutting to specified dimensions. The drug-to-polymer ratio, polymer molecular weight and end-group chemistry (acid or ester end-capped), and manufacturing temperature profile determine drug release duration and completeness. Non-biodegradable implants using polyvinyl alcohol membranes surrounding a drug core are manufactured by precision compression and membrane lamination, with the membrane porosity controlling drug diffusion rate and hence release kinetics. Both implant types require stringent sterility assurance, typically by gamma irradiation, with validation that sterilization does not alter polymer molecular weight distribution or drug crystallinity [33].

5.4 Preparation of Drug-Loaded Contact Lenses

Drug loading of commercial silicone hydrogel contact lenses by soaking in concentrated drug solution is the simplest approach but achieves low and variable drug loading due to the limited drug uptake capacity of hydrated lenses. More effective loading strategies include incorporation of drug-laden nanoparticles or vitamin E nanobarriers within the lens polymer matrix during lens fabrication, creating drug reservoirs that sustain drug release through the wearing period. The vitamin E nanobarrier approach, in which vitamin E aggregates distributed within the silicone hydrogel create a tortuous diffusion path for drug molecules, has demonstrated 100-fold increase in drug release duration compared to soaked lenses for timolol and other small molecule glaucoma drugs [34].

6. Characterization and Evaluation

6.1 Physicochemical Characterization

Ophthalmic formulations require characterization of particle size (for colloidal systems), pH, osmolarity, viscosity, and drug content. The critical quality attributes of ophthalmic nanoparticles include size (100 to 300 nm, confirmed by DLS), PDI (<0.25 for homogeneous preparations), zeta potential (indicative of surface charge and colloidal stability), drug encapsulation efficiency (>70% by ultrafiltration or centrifugation before HPLC quantification), and morphology by TEM. pH must be within 6.0 to 8.0, and osmolarity within 270 to 310 mOsm/kg. In situ gelling formulations require gelation temperature confirmation by rheological measurement of storage modulus (G') transition during temperature ramping from 25 to 37°C [35,36].

6.2 In Vitro Drug Release and Corneal Permeation

Drug release from ophthalmic nanoparticles and in situ gels is assessed using dialysis bag methods in phosphate buffered saline pH 7.4 at 34°C to simulate lacrimal fluid conditions, with sampling at defined time points and drug quantification by HPLC. Corneal permeation is evaluated using excised bovine or

porcine cornea mounted in a modified Franz diffusion cell with donor and receptor compartments simulating lacrimal fluid and aqueous humor composition respectively. The apparent permeability coefficient (Papp) and enhancement ratio relative to the drug in solution are calculated to quantify the permeation-enhancing effect of the nanocarrier or formulation excipients [37].

6.3 Ocular Bioavailability and Pharmacokinetics

In vivo ocular pharmacokinetic studies in rabbits are the most commonly employed preclinical model for topical ophthalmic formulation evaluation. Following topical administration of the test formulation, aqueous humor is sampled at multiple time points by anterior chamber paracentesis under anaesthesia, and drug concentrations are measured by HPLC with UV or mass spectrometry detection. The area under the aqueous humor concentration-time curve (AUC), maximum aqueous humor concentration (Cmax), and time to maximum concentration (Tmax) provide quantitative pharmacokinetic parameters that enable comparison of formulations and calculation of relative bioavailability. Absolute bioavailability relative to intracameral injection is rarely reported in ophthalmic pharmacokinetic studies due to the difficulty of achieving complete mixing of intracameral injections in the anterior chamber [38].

6.4 Ocular Tolerability and Safety

The Draize eye irritation test in albino rabbits, while ethically controversial and increasingly replaced by alternative methods, remains a regulatory requirement for assessment of acute ocular irritation potential of new ophthalmic formulations. In vitro alternatives including the bovine corneal opacity and permeability (BCOP) assay, the isolated chicken eye (ICE) test, and the hen's egg test on the chorioallantoic membrane (HET-CAM) have been validated against Draize test results and are accepted by regulatory agencies as part of a tiered hazard assessment approach. Cell viability assays on human corneal epithelial cell lines provide complementary cytotoxicity data particularly relevant for novel excipients and nanocarrier materials [39].

7. Mechanism of Ocular Drug Delivery

7.1 Corneal Transcellular and Paracellular Transport

Drug permeation through the cornea occurs by two parallel pathways: transcellular permeation, in which drug molecules partition into and diffuse through the lipid bilayer of the apical corneal epithelial cell membrane, traverse the cell cytoplasm, and exit through the basolateral membrane; and paracellular permeation between adjacent corneal epithelial cells through the tight junction complex. Transcellular permeation predominates for lipophilic drugs, with the partition coefficient between octanol and water governing the rate of membrane partitioning. Paracellular permeation is limited to small hydrophilic molecules (typically below 400 Daltons) that can squeeze between tight junction strands, or is enhanced by permeation enhancers including EDTA, surfactants, and chitosan that temporarily disrupt tight junctions [40].

7.2 Nanoparticle Uptake and Transcorneal Transport

Nanoparticles are internalized by corneal epithelial cells through endocytic pathways including clathrin-mediated endocytosis, caveolae-mediated endocytosis, and macropinocytosis, with the predominant pathway depending on nanoparticle size, surface charge, and surface coating. Nanoparticles in the 100 to 200 nm size range are most efficiently internalized by clathrin-mediated endocytosis in corneal epithelial cells. Chitosan-coated nanoparticles trigger transient tight junction opening through activation of protein kinase C-mediated pathways, creating both transcellular (through nanoparticle endocytosis) and paracellular (through tight junction disruption) drug permeation pathways simultaneously [41].

7.3 Drug Distribution in Posterior Segment

Following intravitreal injection or implant drug release, drug molecules distribute through the vitreous humor by diffusion, a process governed by the molecular weight and charge of the drug and by the structure of the vitreous collagen-hyaluronate network. Small molecules with molecular weights below 500 Daltons diffuse relatively freely through the vitreous in hours to days, while large macromolecules including antibody fragments and whole antibodies diffuse over days to weeks and may establish concentration gradients. Drug elimination from the vitreous occurs primarily through the anterior route (aqueous humor turnover through the trabecular meshwork) for small molecules and through the posterior route (across the blood-retinal barrier and into the choroidal circulation) for molecules that can permeate the RPE [42].

8. Therapeutic Applications

8.1 Glaucoma Management

Glaucoma, characterized by progressive optic nerve damage associated with elevated intraocular pressure (IOP), is managed pharmacologically by topical administration of IOP-lowering agents including prostaglandin analogues, beta-adrenergic antagonists, carbonic anhydrase inhibitors, and alpha-2 agonists. The fundamental limitation of topical glaucoma therapy is patient non-adherence to twice-daily or four-times-daily dosing regimens, which is the most important modifiable risk factor for glaucoma progression. Advanced ocular drug delivery approaches including in situ gels, nanoparticles, and sustained-release intracanalicular inserts address this adherence problem by reducing dosing frequency [43,44].

Poloxamer-based in situ gels of timolol maleate demonstrated twofold higher aqueous humor AUC compared to conventional timolol eye drops in rabbit pharmacokinetic studies, attributed to the gel's resistance to nasolacrimal drainage extending the precorneal residence time from minutes to hours. Nanoparticles of latanoprost demonstrated sustained IOP reduction over 72 hours following a single topical application in glaucomatous rabbit models, offering the prospect of twice-weekly rather than once-daily dosing. Bimatoprost sustained-release implant (Durysta, Allergan), approved by the FDA in 2020, is a single-dose biodegradable intracameral implant placed in the anterior chamber angle that releases bimatoprost for approximately 3 to 4 months, eliminating daily drop requirements [45].

8.2 Age-Related Macular Degeneration and Anti-VEGF Therapy

Neovascular (wet) age-related macular degeneration is caused by choroidal neovascularization driven by vascular endothelial growth factor (VEGF) overexpression in the sub-retinal space, leading to subretinal fluid accumulation, haemorrhage, and rapid central visual loss. Monthly or bimonthly intravitreal injection of anti-VEGF biologics — ranibizumab (Lucentis), bevacizumab (Avastin, off-label), aflibercept (Eylea), and brolucizumab (Beovu) — is the standard of care and achieves visual acuity stabilization or improvement in 90 to 95% of treated patients when maintained appropriately. However, the treatment burden of monthly injections — approximately 10 to 12 per year — leads to progressive non-adherence with associated visual loss [46,47].

The Port Delivery System with ranibizumab (PDS, Susvimo, Genentech), approved by the FDA in 2021, is a surgically implanted ocular port device containing a refillable reservoir releasing ranibizumab continuously into the vitreous. The PDS was demonstrated in the ARCHWAY phase 3 clinical trial to maintain non-inferior visual acuity outcomes compared to monthly ranibizumab injections while requiring only biannual (every 6-month) refill procedures, reducing the number of office visits and injections by approximately 90%. This device represents a paradigmatic advance in sustained anti-VEGF therapy and has catalyzed development of competing sustained-release anti-VEGF platforms [48].

8.3 Diabetic Retinopathy and Macular Oedema

Diabetic macular oedema, the most common cause of visual impairment in diabetic retinopathy, is treated with intravitreal anti-VEGF injections or corticosteroid implants. The OZURDEX (dexamethasone 0.7 mg intravitreal implant, Allergan), a biodegradable PLGA rod-shaped implant placed in the vitreous by a 22-gauge applicator, provides sustained dexamethasone release over approximately 6 months, offering an alternative to monthly anti-VEGF injections for diabetic macular oedema, particularly in patients with vitrectomized eyes where intravitreal drug clearance is faster. Iluvien (fluocinolone acetonide 0.19 mg intravitreal implant), non-biodegradable and providing 36 months of sustained corticosteroid release, is approved for chronic diabetic macular oedema [49].

8.4 Dry Eye Disease

Dry eye disease, affecting an estimated 344 million people globally, is treated by lubrication, anti-inflammatory therapy, and secretagogue stimulation depending on disease severity and underlying etiology. Cyclosporine A (cyclosporin) ophthalmic emulsion (Restasis, 0.05%, Allergan) and lifitegrast ophthalmic solution (Xiidra, 5%, Novartis) represent anti-inflammatory approaches targeting T cell-mediated ocular surface inflammation. Novel delivery systems for dry eye including cyclosporine A-loaded nanoparticles, micellar formulations, and lipid-based eye drops have demonstrated superior corneal penetration and drug bioavailability compared to the commercial emulsion formulation in preclinical studies, with several in clinical development as of 2023 [50].

9. Recent Advances

9.1 Suprachoroidal Drug Delivery

The suprachoroidal space — a potential space between the sclera and choroid — has emerged as a novel drug delivery route for posterior segment diseases that achieves high choroidal and retinal drug concentrations through direct drug deposition adjacent to the target tissues without vitreous injection. Triamcinolone acetonide suprachoroidal injection (Xipere, Bausch + Lomb, approved by FDA in 2021) delivers the corticosteroid directly to the suprachoroidal space using a 900-micrometer hollow microinjector, achieving 7- to 17-fold higher choroidal and retinal drug concentrations than intravitreal injection at equivalent doses, with substantially reduced intraocular pressure elevation and cataract formation compared to intravitreal corticosteroids [51].

9.2 Gene Therapy for Ocular Diseases

Adeno-associated virus (AAV)-mediated gene therapy for inherited retinal diseases has advanced rapidly, with voretigene neparvovec (Luxturna, Spark Therapeutics), a subretinal AAV2 vector delivering the RPE65 gene, receiving FDA approval in 2017 for biallelic RPE65 mutation-associated retinal dystrophy. This approval established gene therapy as a clinically viable treatment for ocular disease and catalyzed development of numerous AAV-based gene therapy programs for Leber congenital amaurosis, X-linked retinoschisis, choroideremia, and other inherited retinal dystrophies. Intravitreal delivery of gene therapy vectors, which avoids the surgical risks of subretinal injection, has been advanced by development of engineered AAV capsids (AAV7m8, AAV44.9) with enhanced transduction of inner retinal cells following intravitreal injection [52].

9.3 Bispecific Antibody and Antibody Fragment Delivery

Faricimab (Vabysmo, Roche/Genentech), approved by the FDA in January 2022 for neovascular AMD and diabetic macular oedema, is the first bispecific antibody approved for ophthalmic use, simultaneously targeting VEGF-A and Ang-2 (angiopoietin-2). In phase 3 clinical trials, faricimab demonstrated non-inferior visual outcomes to monthly aflibercept while achieving extended treatment intervals of every 12 or 16 weeks in a substantial proportion of patients. The extended dosing interval of faricimab — 2 to 4 fewer injections per year compared to monthly anti-VEGF therapy — represents a meaningful reduction in treatment burden driven by the dual mechanism of VEGF and Ang-2 blockade [53].

9.4 Exosome and Nanoparticle-Based Retinal Gene Delivery

Non-viral delivery of gene editing tools to the retina represents an emerging direction that could avoid the immunogenicity and manufacturing challenges of viral vectors. Lipid nanoparticle delivery of mRNA encoding Cas9 and sgRNA targeting the VEGFA gene was demonstrated to reduce retinal VEGF levels and laser-induced choroidal neovascularization in mouse models following intravitreal injection, providing proof-of-concept for LNP-mediated retinal gene editing without viral vectors. Exosome-based delivery of mRNA and CRISPR ribonucleoprotein complexes to retinal cells has been reported in preliminary studies, with the natural membrane composition and small size of exosomes potentially enabling diffusion through the vitreous to reach inner retinal cells [54].

10. Comparative Analysis

The selection of an ocular drug delivery approach requires consideration of the target disease (anterior vs posterior segment), the physicochemical properties of the drug (small molecule vs biologic, hydrophilic vs lipophilic), the required duration of drug action (acute vs chronic), and the acceptable level of invasiveness. Conventional eye drops remain the preferred first-line delivery approach for anterior segment conditions owing to their patient familiarity, low cost, and established regulatory precedent, despite their fundamental pharmacokinetic limitations. For conditions requiring sustained anterior segment drug delivery — chronic glaucoma, dry eye maintenance therapy — in situ gels and sustained-release intracanalicular inserts offer meaningful improvements in patient compliance through dosing frequency reduction [55].

For posterior segment diseases, the comparison is fundamentally between intravitreal injection (monthly to quarterly), intravitreal implant (annual to triannual), suprachoroidal injection (biannual), and the Port Delivery System (biannual refill). Monthly intravitreal injection provides maximum flexibility for dose titration and formulation of diverse biologics but imposes the greatest treatment burden. Intravitreal implants provide the longest dosing intervals but are restricted to small molecule drugs for current biodegradable systems, with only the Port Delivery System capable of sustained biologic delivery. Suprachoroidal injection provides a less invasive alternative with enhanced posterior segment targeting compared to intravitreal injection [56].

Table 2: Comparative analysis of ocular drug delivery approaches for posterior segment diseases

Parameter	Intravitreal Injection	Biodegradable Implant	Non-Biodegradable Implant	Port Delivery System	Suprachoroidal Injection
Dosing interval	Monthly–quarterly	3–12 months	12–36 months	6 months (refill)	3–6 months
Drug payload	Small mol + biologics	Small molecules	Small molecules	Biologics (ranibizumab)	Small mol + some biologics
Invasiveness	Moderate	Moderate (injection)	High (surgery)	High (surgical implant)	Low–moderate
Retinal drug concentration	High (acute)	Sustained	Sustained	Sustained	Very high (choroidal)
Approved products	Ranibizumab, aflibercept, faricimab	Ozurdex, Yutiq	Vitrasert, Iluvien	Susvimo	Xipere

Small mol: small molecule.

11. Advantages and Limitations

11.1 Advantages of Advanced Ocular Delivery Systems

- In situ gelling systems provide two- to fourfold improvements in aqueous humor bioavailability compared to conventional eye drops by extending precorneal residence time from minutes to hours, with no increase in dosing inconvenience from the patient perspective
- Nanocarrier-based ophthalmic formulations protect labile drugs from tear fluid enzymatic degradation, improve corneal penetration through mucoadhesion and endocytic uptake, and enable sustained drug release in the precorneal space
- Biodegradable intravitreal implants (Ozurdex, Yutiq) eliminate the treatment burden of monthly injections for posterior segment disease while maintaining therapeutic drug concentrations over three to thirty-six months, with no requirement for surgical removal
- The Port Delivery System enables sustained biologic (antibody) delivery to the vitreous — a feat not achievable by conventional intravitreal implants — reducing anti-VEGF injection frequency from twelve per year to two refills per year
- Suprachoroidal injection achieves 7- to 17-fold higher choroidal and retinal drug concentrations compared to equivalent intravitreal doses, potentially enabling dose reduction and reduced systemic and intraocular side effects
- Contact lens-based drug delivery maintains continuous corneal drug contact during the wearing period, enabling controlled drug release for glaucoma and post-operative inflammation management in a form factor already accepted by contact lens wearers
- Gene therapy delivered to the retina via AAV vectors (Luxturna) provides potentially permanent correction of inherited retinal dystrophies with a single treatment, transforming the treatment paradigm from chronic management to curative therapy

11.2 Limitations

- Nanocarrier-based topical formulations, despite preclinical bioavailability advantages, have not yet demonstrated clinical superiority over conventional formulations in rigorous randomized controlled trials for most indications, and remain investigational for most therapeutic applications
- In situ gelling ophthalmic systems can cause transient blurred vision immediately after instillation due to gel formation at the ocular surface, reducing patient acceptance relative to conventional drops for some patients
- Intravitreal implant insertion requires an office procedure with injection risks (endophthalmitis, retinal detachment, vitreous hemorrhage) equivalent to intravitreal injection, making the reduced injection frequency the principal clinical advantage

- The Port Delivery System requires surgical implantation in the operating room under local anaesthesia with a 2.4 mm sclerotomy, a substantially higher procedural burden than intravitreal injection, limiting its adoption to highly motivated patients with established treatment need
- Drug loading capacity of most contact lens-based delivery systems remains insufficient for drugs requiring milligram-level doses, restricting the technology to potent drugs with microgram therapeutic doses
- Long-term safety data for repeated exposure to novel excipients in nanocarrier ophthalmic formulations — particularly surfactants, cationic polymers, and biodegradable polymers — on the corneal endothelium (which does not regenerate in adults) is limited

12. Clinical Translation and Marketed Products

Ocular drug delivery is one of the most commercially productive areas of pharmaceutical development, with numerous approved products representing diverse delivery technologies across anterior and posterior segment applications. The anti-VEGF intravitreal injection market — led by Lucentis, Eylea, and Vabysmo — is among the largest pharmaceutical market segments globally, with combined global sales exceeding 10 billion USD annually. The approval of sustained-release ocular delivery products including Ozurdex (2009), Iluvien (2011), Durysta (2020), Susvimo (2021), Xipere (2021), and Vabysmo (2022) in the five years to 2023 reflects an acceleration of regulatory approval of novel ocular drug delivery systems [57].

The clinical evidence supporting the efficacy and safety of these approved sustained-release ocular delivery systems is robust, with multiple phase 3 randomized controlled trials demonstrating equivalence or superiority to monthly injection standards of care on visual acuity endpoints. The ARCHWAY trial for the Port Delivery System, the MEAD trial for Ozurdex, and the FAME trial for Iluvien represent landmark phase 3 datasets that established the clinical value of sustained intravitreal drug delivery for AMD and diabetic macular oedema, respectively [58].

Table 3: Clinically approved advanced ocular drug delivery products (selected, as of 2023)

Product	Drug	Technology	Indication	Approval / Key Clinical Data
Ozurdex (Allergan)	Dexamethasone 0.7 mg	PLGA biodegradable implant	DME, BRVO, uveitis	FDA 2009; 6-month sustained release; MEAD trial
Iluvien (Alimera)	Fluocinolone 0.19 mg	Non-biodegradable insert	Chronic DME	FDA 2014 (EU 2012); 36-month release; FAME trial
Durysta (Allergan)	Bimatoprost 10 µg	Biodegradable intracameral	Open-angle glaucoma	FDA 2020; 3–4 month IOP reduction; Phase 3 trial
Susvimo (Genentech)	Ranibizumab 100 mg/mL	Port Delivery System	Neovascular AMD	FDA 2021; 6-month refill; ARCHWAY phase 3
Xipere (Bausch + Lomb)	Triamcinolone 4 mg	Suprachoroidal injection	Uveitic macular oedema	FDA 2021; 7–17× higher choroidal levels vs IVT
Vabysmo (Genentech)	Faricimab 6 mg	Intravitreal injection	AMD, DME	FDA 2022; Q12/Q16 week dosing; TENAYA, LUCERNE trials

DME: diabetic macular oedema; BRVO: branch retinal vein occlusion; AMD: age-related macular degeneration; IOP: intraocular pressure; IVT: intravitreal; Q12/Q16: every 12/16 weeks.

13. Critical Analysis

The ocular drug delivery literature presents a striking contrast between its two principal research domains: the anterior segment topical delivery field, which is characterized by abundant preclinical nanocarrier publications reporting bioavailability improvements in rabbit pharmacokinetic models, and the posterior segment field, which is characterized by robust phase 3 clinical trial data supporting a series of regulatory approvals in the 2009 to 2023 period. This asymmetry — prolific preclinical research in topical delivery but

limited clinical translation, versus rich clinical data in intravitreal delivery — reflects structural differences in the translational pathway for topical versus implantable ocular products.

The rabbit eye model, which is the near-universal preclinical pharmacokinetic model for topical ophthalmic formulations, has several important anatomical differences from the human eye that limit the predictive value of rabbit pharmacokinetic data for human bioavailability. Rabbit eyes lack the dense melanin pigmentation of human uveal tissues that binds melanophilic drugs and creates a drug reservoir effect; rabbit corneal surface area relative to eye volume differs from human; and rabbit blink rate (approximately 6 blinks per minute compared to 15 in humans) substantially reduces the rate of precorneal drug clearance by blink-mediated drainage. Published studies comparing topical ophthalmic bioavailability between rabbits and non-human primates or human volunteers have found that rabbit models consistently overestimate human aqueous humor drug concentrations by factors of 2 to 10 for conventional eye drops and by similar or greater factors for nanocarrier formulations [59].

The reporting of relative rather than absolute ocular bioavailability in the nanoparticle ophthalmic literature obscures the absolute magnitude of drug delivery improvement, which is often clinically trivial despite appearing statistically impressive on a relative scale. A nanoparticle formulation that improves aqueous humor AUC from 0.5 ng/mL·h to 1.5 ng/mL·h has achieved a threefold relative improvement that would be prominently featured in a publication abstract, but the absolute aqueous humor concentrations achieved by both formulations may remain far below the minimum effective concentration for the target disease, making the improvement clinically meaningless. Consistent reporting of absolute drug concentrations alongside relative bioavailability improvements, with explicit comparison to therapeutic drug concentration requirements, would substantially improve the clinical relevance of topical ophthalmic nanoparticle studies [60].

The Port Delivery System, while representing a genuine clinical advance in sustained anti-VEGF delivery, encountered a significant safety signal post-approval: conjunctival erosion over the implant site occurred at higher-than-expected rates in real-world use, leading to a Dear Healthcare Provider letter from Genentech and temporary voluntary US market withdrawal in September 2022 pending redesign of the implant-conjunctival interface. This post-approval safety signal illustrates the limitations of phase 3 clinical trials in detecting device-related complications that become apparent with broader usage in patients with more diverse ocular anatomy and conjunctival health status than trial populations. The Susvimo experience underscores the importance of robust post-marketing surveillance for novel ocular drug delivery device-drug combination products [61].

14. Conclusion

Ocular drug delivery has witnessed remarkable clinical advances in the decade to 2023, with the approval of multiple sustained-release intravitreal products that address the fundamental inadequacy of monthly injection therapy for chronic posterior segment diseases. The Port Delivery System, suprachoroidal injection of triamcinolone, bimanual intracameral bimatoprost implant, and faricimab bispecific antibody represent distinct and complementary innovations that collectively reduce the treatment burden of posterior segment eye diseases while maintaining or improving efficacy relative to monthly injection regimens.

For anterior segment conditions, advanced topical delivery systems including in situ gelling formulations, nanoparticle carriers, and contact lens platforms offer pharmacokinetic advantages over conventional eye drops in preclinical models and present compelling patient compliance benefits through dosing frequency reduction. The translation of these advantages to clinical efficacy in randomized controlled trials remains the critical unresolved challenge, requiring better-validated preclinical pharmacokinetic models, clear definition of the minimum effective intraocular drug concentration for each disease target, and well-designed clinical trials with appropriate pharmacokinetic-pharmacodynamic endpoints.

The emergence of suprachoroidal delivery as a new administration route, the rapid advancement of AAV gene therapy for inherited retinal diseases, non-viral LNP-based retinal gene editing, and exosome-mediated retinal delivery collectively define the frontier of ocular drug delivery research that will occupy the next decade of pharmaceutical investigation and clinical development. The unifying theme across these advances — achieving therapeutic drug concentrations at the retina with minimum patient burden and maximum treatment duration — will continue to drive pharmaceutical innovation in the uniquely challenging and clinically important field of ocular drug delivery.

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