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Review Article

Advanced Ophthalmic Drug Delivery Systems and AI-Assisted Drug Discovery: Current Progress and Future Perspectives

Srinivas Dommeti[1], Seetharam Gude[2]

[1]Strides Pharma Inc, New York, USA, India
[2]Research and Development, Aurobindo Pharma Limited, Hyderabad, India

Corresponding Author: Seetharam Gude
Email: seethasaiofficial@gmail.com

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Abstract

Ophthalmic drug development remains one of the most challenging areas in pharmaceutical research due to the complex anatomy and protective barriers of the eye. Conventional ocular dosage forms, particularly topical formulations, often exhibit poor bioavailability because of rapid tear turnover, blinking, nasolacrimal drainage, and limited corneal permeability. These limitations reduce therapeutic efficiency and necessitate frequent dosing, ultimately affecting patient compliance. In recent years, significant advances have been achieved in the development of innovative ocular drug delivery systems, including ocular implants, hydrogels, nanoparticles, nanomicelles, liposomes, microneedles, iontophoresis, in situ gels, and drug-eluting contact lenses. These technologies aim to improve drug retention, enhance tissue penetration, and provide sustained therapeutic effects for both anterior and posterior segment eye diseases. Simultaneously, artificial intelligence (AI) and digital technologies are transforming ophthalmic drug discovery and development by accelerating target identification, molecular screening, biomarker analysis, and formulation optimization. AI-driven approaches such as machine learning, deep learning, explainable AI, and large language models have shown considerable potential in reducing development timelines and improving predictive accuracy. In addition, additive manufacturing technologies, including three-dimensional printing and hot-melt extrusion, have enabled the development of personalized ophthalmic devices and customized drug delivery systems. Despite these advances, several challenges remain, including manufacturing complexity, regulatory uncertainties, scalability issues, data privacy concerns, and the absence of harmonized global guidelines for AI-assisted therapeutics. This review highlights recent developments in advanced ocular drug delivery systems, emerging AI-based technologies, regulatory perspectives, and future opportunities aimed at improving the treatment of complex ocular diseases and reducing the global burden of visual impairment.

Keywords: Ophthalmic drug delivery, Artificial intelligence, Ocular implants, Nanotechnology, 3D Printing

Introduction:

Drug discovery and development is widely recognized as one of the most complex and resource-intensive processes in modern biomedical science. The journey from identifying a therapeutic target to obtaining regulatory approval often spans decades and requires extensive collaboration between academic institutions, pharmaceutical companies, regulatory bodies, and public–private partnerships. Financially, the process is extremely demanding, with estimates suggesting that bringing a single new drug to market may cost anywhere from approximately $314 million to $4.4 billion, depending on the therapeutic area, development pathway, and success rate across clinical phases. The field of ophthalmology provides a clear example of these challenges. The global market for ophthalmic drugs is expanding rapidly and is projected to reach nearly $66 billion by 2030, largely driven by the growing burden of vision-threatening diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. Despite this commercial growth, translating scientific discoveries into effective ophthalmic therapies remains slow and technically challenging. [1] A notable illustration is the case of bevacizumab, a monoclonal antibody initially developed for cancer treatment. The drug required more than two decades of research and billions of dollars in development before clinicians observed, almost serendipitously, that it could also be beneficial in treating AMD when administered in the eye. This unexpected observation ultimately led to the development of a new class of therapies targeting vascular endothelial growth factor (VEGF). Anti-VEGF drugs have since transformed the management of retinal diseases, including AMD, diabetic retinopathy, and retinal vein occlusion, and have contributed significantly to reducing blindness rates in many parts of the world. Nevertheless, the journey from identifying VEGF as a therapeutic target to securing U.S. Food and Drug Administration (FDA) approval for ophthalmic anti-VEGF treatments required more than three decades of research and clinical testing. Progress in ophthalmic drug development remains relatively limited. Since 2010, only 17 new ophthalmic drugs have received FDA approval, most of which focus on a small group of conditions such as AMD, open-angle glaucoma, and dry eye disease. Many serious ocular disorders still lack effective therapeutic options. For example, geographic atrophy (GA), a late stage of dry AMD, currently has no approved treatment capable of restoring visual acuity or reversing retinal damage. Gene therapy has shown promise in certain inherited retinal disorders; for instance, the therapy Luxturna can improve night vision in individuals with mutations in the RPE65 gene. However, its application is limited to this specific genetic subgroup and therefore benefits only a small fraction of patients. [2] Recognizing the need for innovation, recent research initiatives have attempted to identify the most critical priorities in ophthalmic science. A notable example is the UK Clinical Eye Research Strategy, published in 2024, which highlighted twelve key research themes requiring urgent attention. These themes include prevention of cataracts, improved treatments for microbial keratitis, development of more effective community optometric care pathways, strategies to slow the progression of refractive errors, early detection of childhood visual disorders, and improved therapeutic approaches for glaucoma, neurodegenerative eye diseases, dry AMD, and orbital inflammatory disorders. [3] In recent years, artificial intelligence (AI) has emerged as a powerful tool capable of transforming many aspects of the drug discovery pipeline. AI encompasses a broad collection of computational methods, including machine learning (ML) and deep learning (DL) algorithms, that can process extremely large and complex datasets. These models are capable of recognizing hidden patterns within biological data, generating predictive models, and guiding decision-making in ways that were previously impossible with traditional experimental methods. In the context of pharmaceutical research, AI can assist scientists in designing new molecules, predicting drug–target interactions, estimating pharmacokinetic and toxicity profiles, and optimizing clinical trial design. Several recent examples demonstrate the transformative potential of AI-assisted drug discovery. One well-known case is DSP-1181, a drug candidate developed for the treatment of obsessive-compulsive disorder. The compound was designed through a collaboration between Sumitomo Dainippon Pharma and the AI-driven biotechnology company Exscientia. Using advanced machine learning algorithms, researchers were able to optimize the compound's chemical structure, pharmacological properties, and safety characteristics in just 12 months, a remarkably short timeframe compared with the typical five-year period often required for early drug discovery stages. [4] Another groundbreaking example is Halicin, an antibiotic identified using an AI model developed at the Massachusetts Institute of Technology (MIT). By screening a virtual library containing more than 100 million chemical compounds, the AI system identified a molecule with a completely novel structure that demonstrated potent activity against several antibiotic-resistant bacterial strains. This discovery highlighted how AI-based approaches can dramatically accelerate the identification of promising therapeutic molecules compared with traditional laboratory

screening techniques. Growing evidence suggests that integrating AI into early drug discovery could reduce development timelines by more than 60%, while also improving the probability of success in clinical trials. This improvement is particularly notable in biologics and protein-based therapeutics, where predictive modeling can enhance the evaluation of efficacy, safety, and manufacturability before costly experimental testing begins. Beyond traditional machine learning systems, the emergence of large language models (LLMs) and vision–language models (VLMs) has further expanded the capabilities of AI in biomedical research. These advanced models are capable of analyzing vast amounts of biomedical literature, generating hypotheses, predicting drug–target interactions, and even designing entirely new molecular structures. By integrating information from chemical, genomic, and clinical datasets, such systems can assist researchers in making more informed decisions during the earliest phases of drug development, including biomarker discovery and clinical trial planning. [5] The need for accelerated innovation in ophthalmic medicine becomes even more evident when considering the global burden of visual impairment. According to World Health Organization (WHO) data released in 2023, approximately 2.2 billion people worldwide are affected by near or distance vision impairment. Alarmingly, nearly half of these cases remain untreated or could potentially have been prevented with appropriate interventions. The societal and economic consequences of vision loss are immense, with global productivity losses estimated to reach $411 billion annually. The situation is also concerning in the United States, where ocular disorders affect a substantial portion of the population. Recent estimates indicate that around 90 million Americans aged 40 years and older experience some form of vision impairment or eye disease. This represents more than 60% of individuals within that age group. The causes of vision loss are diverse and multifactorial, but several major conditions account for a large proportion of cases, including age-related macular degeneration, glaucoma, cataracts, diabetic retinopathy, and retinal vein occlusion. Without effective management, these conditions can progressively damage ocular tissues and ultimately lead to permanent blindness. Although the pharmaceutical industry has made notable advances in the prevention and management of eye diseases, current therapies often fall short of eliminating or reversing these conditions. One of the central challenges in ophthalmic drug development lies in delivering therapeutically effective drug concentrations to the appropriate tissues within the eye. The eye possesses multiple protective barriers that limit drug penetration, making efficient drug delivery particularly difficult. [6]

Most currently available ophthalmic medications are administered as topical formulations, including eye drops, suspensions, emulsions, and ointments. While these formulations are convenient and noninvasive, they suffer from extremely low drug bioavailability. Several physiological factors contribute to this limitation, including rapid tear turnover, blinking, drainage through the nasolacrimal duct, nonproductive absorption through conjunctival tissues, and the limited permeability of the corneal membrane. As a result, topically administered drugs typically remain in the tear film for only one to three minutes, and less than 5% of the administered dose actually penetrates ocular tissues [7]. These pharmacokinetic limitations significantly reduce therapeutic effectiveness, particularly when attempting to treat diseases affecting deeper ocular structures. Topical formulations are generally effective for conditions affecting the anterior segment of the eye, such as conjunctivitis or corneal inflammation. However, they are largely ineffective for diseases of the posterior segment, which includes the retina, vitreous humor, and choroid. [8] Posterior segment diseases represent one of the leading causes of vision impairment in developed countries. Treating these conditions is especially challenging because drugs must penetrate multiple anatomical barriers to reach retinal tissues. In recent years, the intravitreal injection (IVI) route has become increasingly common for delivering drugs directly into the vitreous cavity, allowing therapeutic agents to reach retinal targets more effectively. Several intravitreal products, including injectable suspensions, solutions, and sustained-release implants, have received approval from the U.S. FDA [9]. Despite these advances, the number of available ophthalmic drugs remains relatively small compared with medications developed for other routes of administration, such as oral therapies. This disparity highlights the urgent need for innovative drug delivery technologies capable of overcoming ocular barriers and improving drug residence time within the eye. Consequently, researchers are actively exploring a range of next-generation ocular drug delivery systems, including nanoparticle-based carriers, biodegradable implants, in situ forming gels, microneedle systems, and gene-based therapeutics. These emerging technologies aim to enhance drug penetration, prolong therapeutic effects, and reduce the need for frequent invasive procedures such as repeated intravitreal injections [10]. Equally important is the need to carefully evaluate the manufacturing, scalability, and regulatory considerations associated with these advanced delivery systems. Successful translation from laboratory

Table 1. Overview of Novel Ophthalmic Therapeutics Approved by the U.S. FDA (CDER) Between 2010 and 2025

Drug Molecule	Commercial Product	Pharmacological Target / Mode of Action	Therapeutic Indication	Year Approved by FDA	Year Approved by EMA
Perfluorohexyloctane	Miebo	Semifluorinated alkane that stabilizes the tear film lipid layer	Dry eye disease	2023	Not approved
Lotilaner	Xdemvy	Antiparasitic agent targeting ectoparasites	Demodex blepharitis	2023	Not approved
Avacincaptad pegol	Izervay	Aptamer inhibitor targeting complement component C5	Geographic atrophy associated with AMD	2023	Not approved
Tebentafusp	Kimmtrak	Bispecific T-cell engager linking gp100 peptide–HLA complex with CD3	Uveal melanoma	2022	2022
Faricimab	Vabysmo	Dual-target monoclonal antibody inhibiting VEGF-A and ANG2 pathways	Neovascular AMD and diabetic macular edema	2022	2022
Omidenepag isopropyl	Omlonti	Selective agonist of the prostaglandin E2 receptor	Open-angle glaucoma or ocular hypertension	2022	Not approved
Satralizumab	Enspryng	Monoclonal antibody blocking interleukin-6 receptor signaling	Neuromyelitis optica spectrum disorder	2020	2021
Teprotumumab	Tepezza	IGF-1 receptor–targeted monoclonal antibody	Thyroid eye disease	2020	Not approved
Brolucizumab	Beovu	Anti-VEGF monoclonal antibody fragment	Neovascular age-related macular degeneration	2019	2020
Cenegermin	Oxervate	Recombinant human nerve growth factor (NGF)	Neurotrophic keratitis	2018	2017
Latanoprostenebunod	Vyzulta	Nitric oxide–donating prostaglandin analog	Reduction of intraocular pressure	2017	Not approved
Netarsudil	Rhopressa	Rho-associated protein kinase (ROCK) inhibitor	Open-angle glaucoma or ocular hypertension	2017	2019 (marketed as Rhopressa)
Lifitegrast	Xiidra	LFA-1 antagonist that blocks T-cell mediated inflammation	Dry eye disease	2016	Not approved
Tafluprost	Zioptan	Selective prostaglandin F receptor agonist	Open-angle glaucoma or ocular hypertension	2012	2008 (marketed as Taflotan)
Ocriplasmin	Jetrea	Recombinant truncated form of human plasmin enzyme	Symptomatic vitreomacular adhesion	2012	2013
Aflibercept	Eylea	Recombinant fusion protein binding VEGF-A and placental growth factor	Neovascular age-related macular degeneration	2011	2012
Alcaftadine	Lastacaft	Histamine H1 receptor antagonist	Allergic conjunctivitis	2010	Not approved

research to clinical application will require multidisciplinary collaboration involving pharmaceutical scientists, clinicians, engineers, and regulatory experts. By addressing these challenges, it may be possible to significantly expand the therapeutic arsenal available for treating complex ocular diseases, particularly those affecting the posterior segment of the eye. [11]

Barriers to Ocular Drug Delivery:

The eye is a highly specialized organ responsible for vision and is considered an immune-privileged site, meaning it has protective mechanisms that limit inflammation and protect delicate visual tissues. Its complex structure consists of specialized tissues, nerves, muscles, glands, and a well-organized vascular system. While these features are essential for maintaining normal ocular function, they also create significant challenges for effective drug delivery. From a pharmaceutical perspective, the anatomical and physiological characteristics of the eye act as protective barriers that restrict the entry, distribution, and retention of therapeutic agents. These barriers are designed to prevent harmful substances from entering ocular tissues, but they can also reduce the effectiveness of administered medications. [12]

Although the anatomy of the eye has been widely described in scientific literature, this section focuses specifically on the barriers that interfere with ocular drug delivery and briefly highlights possible approaches to overcome them. Understanding these barriers is essential for the development of effective ophthalmic treatments delivered through routes such as topical administration, subconjunctival injection, intravitreal delivery, and subretinal therapy. In general, ocular barriers can be broadly categorized into static barriers and dynamic barriers. Static barriers include the physical structures of the eye that limit drug penetration, whereas dynamic barriers involve physiological processes such as tear turnover, blinking, and blood circulation that remove drugs from the ocular surface. Together, these barriers strongly influence drug stability, distribution, and overall therapeutic effectiveness in ocular treatments. [13]

Static Barriers:

Static barriers in the eye refer to the structural components that physically limit the penetration and distribution of drugs within ocular tissues. These barriers arise from the inherent anatomical features and composition of the eye. Among them, the cornea and the blood–ocular barriers are considered the most important obstacles that influence ophthalmic drug delivery. The cornea, which forms the transparent front surface of the eye, acts as the first and most significant barrier for drugs administered topically [14]. It consists of multiple layers with both hydrophilic and lipophilic characteristics, making drug permeation highly dependent on the physicochemical properties of the drug molecule. In general, compounds with moderate lipophilicity (logP values between about 2 and 4) tend to penetrate the cornea more effectively. Tight junctions between epithelial cells restrict the passage of hydrophilic or highly polar molecules, making drug solubility and formulation characteristics critical for successful delivery. Beneath the corneal epithelium lies the Bowman's layer, a thin acellular membrane measuring roughly 8–12 μm in thickness. Although it was once believed to provide structural protection and regulate the movement of large molecules, more recent studies suggest that its direct influence on drug transport is relatively limited. Interestingly, research has shown that the thickness of Bowman's layer gradually decreases with age and has minimal regenerative capacity, which may have implications for future ocular drug delivery strategies. [15] The corneal stroma, located below Bowman's layer, accounts for nearly 90% of the total corneal thickness and is primarily hydrophilic in nature. Because of its fluid-like structure, it generally allows the diffusion of many polar molecules, including relatively large compounds. However, hydrophobic drugs may experience greater resistance when moving through this layer. In addition, the stroma can act as a temporary drug reservoir, retaining compounds that have crossed the epithelium. While this effect can be beneficial for treating corneal conditions, it may limit drug availability in deeper ocular tissues such as the retina. Between the stroma and the inner endothelial layer lies Descemet's membrane, which serves as a thin supportive structure. This membrane usually does not significantly restrict small drug molecules, but it can hinder the passage of larger macromolecules or particulate drug systems. [16] The innermost corneal layer is the corneal endothelium, which plays a key role in maintaining corneal hydration and transparency. Endothelial cells actively regulate fluid balance through ion transport systems, including sodium–potassium ATPase pumps and other transport proteins. Although the endothelium is generally more permeable than the corneal epithelium, drug movement across this layer can still be influenced by molecular size and other physicochemical properties. In addition to the cornea, the eye contains specialized vascular barriers that further restrict drug entry from the bloodstream [17]. These include the blood–aqueous barrier and the blood–retinal barrier, both of which tightly regulate the exchange of sub-

stances between systemic circulation and ocular tissues. The blood–aqueous barrier, formed by the epithelium of the ciliary body and blood vessels of the iris, controls the composition of the aqueous humor. The blood–retinal barrier, composed of retinal pigment epithelial cells and retinal vascular endothelial cells, protects the neural retina. Together, these barriers significantly limit the effectiveness of drugs administered through systemic routes. [18]

Dynamic Barriers:

In addition to the structural barriers of the eye, several physiological processes actively limit the effectiveness of ocular drug delivery. These dynamic barriers function by continuously removing or diluting drugs from the ocular surface, thereby reducing the time available for drug absorption [19]. Important dynamic barriers include the tear film, blinking activity, nasolacrimal drainage, and conjunctival blood circulation. The tear film is one of the primary factors influencing drug retention on the ocular surface. This thin protective layer, approximately 6 μm thick, plays a crucial role in lubricating the eye and maintaining a smooth optical surface over the cornea, which is necessary for clear vision. It is composed of three layers lipid, aqueous, and mucin, each contributing to tear stability and ocular protection. The composition of tears can vary depending on the stimulus that triggers tear production, such as emotional responses or irritation. This variability can influence how drugs behave when applied to the eye. Additionally, the tear film has a pH typically ranging between 6.5 and 7.6, which must be considered during formulation development to ensure drug stability and minimize irritation. Tears also contain protective proteins such as lysozyme, lactoferrin, and immunoglobulin A, which provide antimicrobial defense but may interact with certain drug molecules. [20] Another challenge associated with the tear film is its rapid turnover. The total tear volume is relatively small, about 7–9 μL, and tear secretion occurs at a rate of roughly 1 μL per minute. This means the tear layer is refreshed within a short time. Blinking further accelerates this process, as the human eye may blink multiple times per minute. Although these mechanisms are essential for maintaining ocular health, they significantly reduce the residence time of drugs applied to the eye, making it difficult for medications to remain on the surface long enough to be absorbed effectively [21]. The nasolacrimal drainage system also plays an important role in drug loss following topical administration. This system removes excess tear fluid from the ocular surface and drains it into the nasal cavity. Tears first enter small openings called puncta located on the inner side of the eyelids. From there, fluid passes through narrow channels known as canaliculi, which join to form the lacrimal sac before draining into the nasolacrimal duct and eventually the nasal cavity [22]. Because this drainage process is continuous, a significant portion of an administered eye drop can be rapidly cleared from the eye. In many cases, up to 80% of the instilled drug may be lost within 15–30 seconds after administration. Larger drop volumes can further increase drug loss by triggering reflex tearing and overflow. In addition, drugs that enter the nasolacrimal pathway may be absorbed through the nasal mucosa, potentially leading to systemic exposure and unwanted side effects. The conjunctiva represents another dynamic factor affecting ocular drug distribution. This thin mucous membrane covers the front of the eye and lines the inner surfaces of the eyelids. It contains a dense network of blood vessels that supply nutrients to the ocular surface. While the conjunctiva can allow certain drugs to penetrate its epithelial layer, the underlying blood vessels can rapidly transport these molecules into the systemic circulation. As a result, the amount of drug reaching deeper ocular tissues may be reduced, and the risk of systemic absorption may increase. Taken together, these dynamic barriers significantly influence the fate of drugs administered to the eye. Their combined effects often lead to rapid drug elimination and limited ocular bioavailability. For this reason, the development of effective ophthalmic therapies frequently requires innovative formulation approaches or specialized delivery systems designed to prolong drug residence time and improve drug penetration into target ocular tissues. [23]

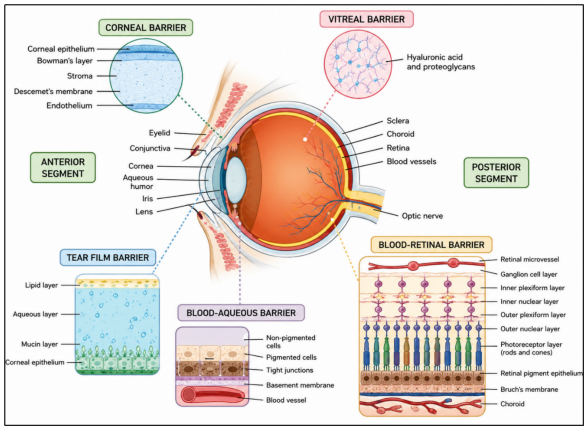

Figure 1. Drug delivery barriers in ocular routes

Advanced Ocular Drug Delivery Strategies:

Ocular Implants

Ocular implants have emerged as an important innovation in ophthalmic drug delivery, providing an alternative to traditional methods such as eye drops or

repeated injections. These implantable systems are specifically designed to release therapeutic agents at a targeted ocular site over a controlled period of time [24]. By maintaining sustained drug levels directly at the site of action, ocular implants can reduce the frequency of drug administration and minimize the need for repeated invasive procedures, which may otherwise increase the risk of infection or inflammation. One of the key advantages of ocular implants is their ability to deliver drugs locally while maintaining stable therapeutic concentrations for extended periods. The placement of the implant depends on the disease location within the eye. For disorders affecting the anterior segment, implants are often positioned in the subconjunctival region, whereas diseases of the posterior segment are typically treated using intravitreal or suprachoroidal implants. Another option is intrascleral implantation, which can be used for both anterior and posterior segment conditions [25]. Because these devices are positioned close to the target tissue, they can enhance drug delivery while reducing systemic exposure. [26]

The implantation procedure varies according to the location of delivery. Subconjunctival implants are usually inserted onto the sclera through a small incision in the conjunctiva. Intrascleral implants are placed within a small pocket created in the scleral tissue, typically at about half the scleral thickness, which allows drug diffusion toward posterior ocular tissues with limited systemic absorption. Intravitreal implants are introduced directly into the vitreous cavity using specialized applicators. This approach provides direct access to retinal tissues and eliminates the need for sutures, as the device can be delivered through a needle or small sclerotomy. The pars plana region is commonly selected as the insertion site because it minimizes the risk of damage to sensitive ocular structures. Based on the materials used and the mechanism of drug release, ocular implants are generally classified into biodegradable and non-biodegradable systems [27]. Non-biodegradable implants are capable of releasing drugs at a controlled rate for extended durations, sometimes lasting several years. However, these devices must eventually be removed or replaced once the drug supply is exhausted. In contrast, biodegradable implants gradually degrade within the body after delivering the drug, eliminating the need for surgical removal [28]. They can also be manufactured in various shapes and may allow implantation procedures to be performed more easily. Several ocular implant products have already received approval from the U.S. Food and Drug Administration (FDA). Among these, most non-biodegradable implants rely on polymers such as polyvinyl alcohol (PVA) to regulate drug release. Biodegradable implants are typically composed of bioabsorbable polymers, including poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA). One recently approved implant is iDose TR, a small travoprost-containing device designed to continuously release medication for glaucoma management. Another notable system is Suvismo, a refillable intravitreal implant that delivers ranibizumab through a port delivery system, allowing refilling approximately every six months. [29]

In Situ Gels

In situ gelling systems represent an advanced approach for ocular drug delivery. These formulations are typically administered as liquid eye drops, but once they reach the ocular surface, they undergo a transformation into a semi-solid gel. This phase transition occurs within the conjunctival sac (ocular cul-de-sac) and can be triggered by environmental factors such as changes in temperature, pH, ionic concentration, or light exposure. After gel formation, the formulation becomes more viscous and remains in contact with ocular tissues for a longer time compared with conventional eye drops. The polymers used in these systems play a key role in the gelation process. They create a protective and adhesive matrix over the ocular surface, allowing the drug to remain at the site of action for extended periods. Because of this prolonged residence time, in situ gels enhance drug absorption and reduce the need for frequent administration. The viscoelastic properties of the gel enable it to adhere effectively to ocular tissues such as the cornea and conjunctiva, improving drug–tissue interaction and facilitating diffusion through epithelial barriers. In addition, many in situ gels are designed to release the drug gradually, which helps maintain therapeutic drug levels over a sustained period. As a result, these systems have the potential to overcome some major limitations of traditional ophthalmic dosage forms, including rapid drug elimination and poor bioavailability. [30] Recent research has increasingly focused on thermosensitive in situ gels, which respond to temperature changes after administration. These systems remain in liquid form at room or storage temperature but form a gel once exposed to the physiological temperature of the eye. A variety of polymers have been explored for this purpose, including chitosan, polyethylene glycol, polycaprolactone, poloxamers, polylactide, and polyglycolide. These materials can self-assemble into temperature-dependent micellar structures that transform into gels when the temperature increases, thereby improving drug retention and potentially enhancing delivery to both the anterior and posterior segments of the eye. Several ex-

Table 2. Approved Ocular Drug Implants and Sustained-Release Delivery Systems for the Treatment of Retinal and Glaucoma-Related Disorders

Active Drug	Brand / Product Name	Dose Strength	Therapeutic Use	Delivery Route	Duration of Therapeutic Effect	Release / Control System	Approval Year
Ganciclovir	Vitrasert	4.5 mg	Treatment of cytomegalovirus (CMV) retinitis	Intraocular implant	Approximately 5–8 months	Polyvinyl alcohol (PVA) and ethylene-vinyl acetate (EVA) polymers	1996
Fluocinolone acetonide	Retisert	0.59 mg	Management of chronic uveitis	Intravitreal implant	Around 30 months	Polyvinyl alcohol (PVA) matrix	2005
Dexamethasone	Ozurdex	0.7 mg	Diabetic macular edema (DME), retinal vein occlusion (RVO), and uveitis	Intravitreal implant	Up to 6 months depending on disease condition	Poly (lactic-co-glycolic acid) (PLGA) biodegradable system	2009
Fluocinolone acetonide	Iluvien	0.19 mg	Treatment of diabetic macular edema	Intravitreal implant	Nearly 36 months	Polyimide tube with PVA and silicone adhesive components	2014
Fluocinolone acetonide	Yutiq	0.18 mg	Therapy for non-infectious uveitis	Intravitreal implant	Up to 36 months	Polyimide tubing combined with PVA and silicone adhesive	2018
Bimatoprost	Durysta	10 μg	Reduction of intraocular pressure (IOP) in glaucoma	Ophthalmic / intracameral implant	Several months	Biodegradable polymers including PLGA, PDLA, PDLLA, and PEG 3350	2020
Ranibizumab	Susvimo	2 mg	Management of neovascular (wet) age-related macular degeneration	Intravitreal port delivery system	Up to 6 months between refills	Implantable port-based drug delivery device	2021
Travoprost	iDose TR	75 μg	Lowering intraocular pressure	Intracameral implant	About 3 months	Titanium reservoir with a semipermeable membrane coating	2023

perimental studies have demonstrated the potential of this technology. For example, formulations containing gatifloxacin prepared with alginate and hydroxypropyl methylcellulose (HPMC) showed favorable rheological properties and effective gel formation in simulated tear fluid. The optimized composition provided controlled drug release without irritating ocular tissues. In another study, researchers developed a microemulsion-based in situ gel containing betamethasone and moxifloxacin for use after ocular surgery. This formulation remained liquid during storage but gelled at ocular surface temperature, enabling accurate dosing and sustained drug release. Ex vivo experiments using porcine corneal tissue indicated improved drug permeability compared with conventional formulations. Other investigations have incorporated drug-loaded nanoparticles within in situ gels to further enhance performance. For instance, moxifloxacin-loaded nanoparticle gels demonstrated prolonged drug release and effective antibacterial activity against keratitis. Experimental studies also confirmed good ocular tolerance and reduced bacterial load in infected corneal tissue. Similarly, temperature-responsive gel systems have been explored for delivering cysteamine, a drug used to treat cystinosis. These systems were able to release the drug gradually over several hours while promoting efficient corneal absorption with minimal systemic exposure. [31]

Nanomicelles

Nanomicelles are nanosized carriers typically ranging from about 10 to 100 nm. They consist of a hydrophobic core formed by fatty acyl chains and a hydrophilic outer shell composed of polar head groups. Because of this amphiphilic structure, nanomicelles can solubilize both hydrophilic and poorly water-soluble drugs, making them effective delivery vehicles for targeting both the anterior and posterior segments of the eye. Previous research has highlighted important considerations for using nanomicelles in ocular drug delivery, particularly regarding their ability to cross ocular barriers. [32] These systems offer several advantages, including

simple preparation methods, small particle size, and a high capacity for drug encapsulation. Such features contribute to improved drug stability, enhanced ocular bioavailability, and better therapeutic outcomes. In addition, nanomicelles are increasingly being explored for ocular gene delivery applications. Particle size plays a crucial role in their performance, as smaller nanomicelles generally exhibit better permeability and more efficient transport across ocular tissues. Recent experimental studies have demonstrated the potential of nanomicelles in improving drug delivery in ocular disease models. Their amphiphilic nature, nanoscale size, and efficient drug-loading ability enable them to significantly increase the solubility and bioavailability of poorly soluble drugs. For example, Ping Lu and colleagues developed TPGS-based nanomicelles loaded with butenafine (BTF) for the treatment of fungal keratitis [33]. The formulation dramatically increased BTF solubility and improved its permeability across the cornea. In animal models, this nanomicellar system produced better therapeutic outcomes than conventional formulations, mainly due to prolonged retention on the ocular surface and improved drug penetration into corneal tissues. Overall, nanomicelle-based systems represent a promising strategy for overcoming ocular drug delivery barriers and enhancing treatment effectiveness for various eye disorders. [34]

Microparticles

Microparticles represent an important strategy in ocular drug delivery because they can provide prolonged drug release and improved ocular bioavailability. These tiny polymer-based particles, typically ranging from 1–1000 μm, are dispersed in a liquid medium and can encapsulate drugs either by physical entrapment within the polymer matrix or by chemical attachment to the polymer structure. Based on their structure, microparticles are mainly classified as microspheres and microcapsules. [35] After topical administration, microparticles tend to settle in the ocular cul-de-sac, which helps extend the precorneal residence time of the drug. The medication is then released gradually through mechanisms such as diffusion, polymer degradation, or chemical reactions. This sustained release reduces the need for frequent dosing and enhances the overall therapeutic availability of the drug in the eye. However, the relatively larger particle size may sometimes cause ocular irritation. Therefore, polymers used for ophthalmic microparticles should ideally be biodegradable, biocompatible, and capable of adhering to ocular tissues. Typically, only small volumes (50–100 μL) of microparticle formulations can be safely injected into the eye. Several studies highlight the therapeutic potential of microparticle systems. For instance, PLGA-based microparticles containing EPO-R76E, a modified form of erythropoietin, demonstrated neuroprotective effects on retinal neurons and optic nerve axons without significantly increasing hematocrit levels in glaucoma models. Another investigation utilized PLGA microspheres loaded with dexamethasone, melatonin, and coenzyme Q10, which showed notable neuroprotective effects in a mouse model of chronic ocular hypertension after a single intravitreal injection [36]. In addition, dexamethasone-loaded PLGA microspheres were reported to effectively reduce inflammation in rabbit eyes following lipopolysaccharide-induced ocular inflammation within 30 days of treatment. [34]

Liposomes

Liposomes are microscopic vesicular carriers composed of one or more phospholipid bilayers surrounding aqueous compartments. Based on the number of lipid layers and particle size, liposomes are commonly classified into three types: multilamellar vesicles (MLVs), which contain multiple lipid bilayers and usually exceed 300 nm in size; small unilamellar vesicles (SUVs), typically ranging from 10–100 nm; and large unilamellar vesicles (LUVs), generally measuring between 100–300 nm. In ocular drug delivery, liposomes are particularly advantageous because their lipid composition closely resembles biological membranes, enabling them to interact effectively with the corneal and conjunctival surfaces and enhance drug absorption [35]. This system is especially useful for drugs with poor solubility, limited permeability, low partition coefficients, or relatively large molecular weights. The effectiveness of liposomes in ophthalmic applications is largely attributed to their excellent biocompatibility and their ability to encapsulate both hydrophilic and hydrophobic therapeutic agents. Several studies have reported their potential in delivering drugs to both anterior and posterior segments of the eye. Surface charge also plays an important role in determining their performance; positively charged liposomes tend to exhibit improved adherence and absorption on the negatively charged corneal surface compared with neutral or negatively charged vesicles. In addition, liposomes are generally biodegradable and can provide controlled or sustained drug release. Despite these advantages, certain limitations exist. For example, liposomal suspensions may sometimes cause temporary vitreous opacity or blurred vision. Moreover, in inflamed ocular tissues, liposomes may exhibit shorter half-lives, possibly due to changes in the blood–retinal barrier and increased degradation by infiltrating inflamma-

tory cells. [36] Recent research has explored various liposomal formulations for topical ocular therapy. For instance, a study conducted in 2022 developed a liposomal formulation of fluconazole and compared it with a conventional commercial product. The liposomal system demonstrated sustained drug release with zero-order kinetics and showed higher ex vivo corneal permeation. Pharmacokinetic analysis indicated significant increases in both the area under the curve and the mean residence time compared with the marketed formulation, while preclinical studies reported no ocular irritation or hemolytic effects [37]. In another investigation, liposomes carrying the poorly soluble antiglaucoma drug acetazolamide were incorporated into a hydroxypropyl methylcellulose (HPMC)-based formulation. This hybrid system markedly improved ocular bioavailability, mainly due to increased viscosity from HPMC, which prolonged precorneal residence time, and a dispersion medium designed to mimic the natural tear film environment. Studies have also examined how liposome characteristics influence retinal delivery. Factors such as particle size, surface coating, and charge significantly affect retinal penetration. Experimental findings suggest that smaller liposomes, around 50 nm in diameter, can penetrate retinal tissues more efficiently than larger vesicles, while PEGylation and negatively charged surfaces help achieve more uniform retinal distribution. [38] Although liposomal drug delivery has shown considerable promise, the development and regulatory approval of such formulations remain challenging. Only a limited number of liposomal products have received approval from the U.S. Food and Drug Administration (FDA), largely due to the complexity of their formulation and manufacturing processes. The FDA issued specific guidance for liposomal drug products covering chemistry, manufacturing, controls, pharmacokinetics, and labeling requirements. Currently, only a few liposome-based products are available for ocular use. For example, Visudyne® contains verteporfin and is administered intravenously for photodynamic therapy in conditions such as age-related macular degeneration and choroidal neovascularization. Another product, Tears Again®, is a liposomal spray designed to stabilize the tear film and provide lubrication in patients with dry eye disease. Clinical studies have demonstrated that this liposomal spray offers improved symptomatic relief compared with some conventional ocular lubricants. [39]

Nanoparticles

Polymeric nanoparticles are colloidal carriers typically smaller than 1000 nm and are prepared using biodegradable polymers. In ocular drug delivery, the particle size plays a critical role in determining drug loading, stability, and distribution. Generally, nanoparticles ranging from 200–400 nm are considered optimal for topical ophthalmic administration because they can be efficiently absorbed through the cornea and conjunctiva [40]. Their small size helps reduce ocular irritation, enhance penetration across ocular barriers, and improve interaction with the mucosal surface of the eye. Surface charge also influences their performance; positively charged nanoparticles often remain longer on the ocular surface due to electrostatic attraction with negatively charged ocular tissues. A variety of natural and synthetic polymers are used to develop these systems, including PLA, PLGA, chitosan, sodium alginate, albumin, and polycaprolactone. Structurally, nanoparticles are generally classified into nanocapsules and nanospheres. Nanocapsules consist of a core surrounded by a polymeric shell where the drug is enclosed, whereas nanospheres have the drug uniformly dispersed throughout the polymer matrix. These systems provide advantages such as improved drug protection, controlled release, and enhanced drug distribution within ocular tissues. [41] Due to their ability to provide sustained drug delivery and minimize irritation, nanoparticles are widely explored for treating both anterior and posterior eye diseases. Their prolonged drug release profile can reduce the need for frequent dosing, which improves patient adherence. To further enhance ocular retention, researchers have also developed mucoadhesive nanoparticles that can remain on the ocular surface for extended periods. Recent studies highlight the potential of these systems [42]. For example, Khalil et al. designed a hybrid ocular insert containing azithromycin-loaded PLGA nanoparticles embedded in electrospun poly(N-vinyl pyrrolidone) nanofibers [107]. This biodegradable and mucoadhesive system enabled drug release for more than ten days, reducing dosing frequency and improving therapeutic effectiveness. In another study, tacrolimus-loaded nanoparticles prepared with gellan gum using ionotropic gelation demonstrated prolonged precorneal retention and sustained drug release for the treatment of dry eye disease. Safety evaluations confirmed their ocular compatibility. Additionally, chitin-based nanoparticles have been investigated for delivering fluconazole, showing a controlled two-stage release profile with minimal drug release during the initial 48 hours. Overall, nanoparticle-based systems represent a promising strategy for achieving long-lasting ocular drug delivery. [42]

Iontophoresis

Ocular iontophoresis is an emerging non-invasive technique for delivering drugs to both the anterior and posterior segments of the eye. This method uses a mild electrical current to drive charged drug molecules across ocular tissues. Drug transport mainly occurs through two mechanisms: electro-osmosis and electromigration. During the procedure, an electrode with the same charge as the drug is placed near the eye to facilitate delivery, while a counter electrode with the opposite charge is positioned elsewhere on the body to complete the electrical circuit [43]. In this process, the drug solution also functions as the conductive medium. Although clinical studies in humans remain limited, several animal studies have demonstrated that both transcorneal and transscleral iontophoresis can effectively deliver various ophthalmic agents, including oligonucleotides. Compared with intravitreal injections or surgical implants, iontophoresis is less invasive and avoids many associated complications. However, it does not significantly prolong the intrinsic half-life of the drug. Experimental studies have shown that transscleral iontophoresis can facilitate the delivery of anti-VEGF agents to the retina and choroid. For example, applying a current density of about 6.25 mA/cm² has been reported to increase corneal drug accumulation to approximately 120 ng/mg, creating a depot that slowly releases the drug into the aqueous humor. [44] Three main approaches to ocular iontophoresis have been developed: transcorneal, transscleral, and corneoscleral iontophoresis. The sclera is particularly suitable for drug transport to the posterior segment due to its relatively high permeability, large surface area, and high hydration level. Compared with conventional eye drops, iontophoresis can improve drug penetration and reduce rapid drug clearance. It may also enhance patient compliance compared with repeated intraocular injections [45]. However, the method has certain limitations, such as the need for repeated treatments, possible mild discomfort during application, and limited duration of drug action. Recent research has explored combining iontophoresis with nanoparticle-based drug delivery systems. For instance, latanoprost-loaded PLGA nanoparticles have been delivered using iontophoresis for glaucoma therapy. In vivo studies indicated that nanoparticles around 300 nm in size produced the most prolonged therapeutic response. This approach extended the drug's effect for more than seven days and demonstrated significantly greater efficacy compared with the commercial latanoprost formulation Xalatan®. Several devices have been developed to support ocular iontophoretic delivery. The OcuPhor™ system, designed for transscleral drug delivery, includes an applicator, dispersive electrode, and a dose controller to regulate the electrical current [46]. Another system, Visulex™, enables targeted movement of ionized molecules across the sclera. Iontophoresis has also been investigated for the delivery of several antibiotics, such as gentamicin, tobramycin, and ciprofloxacin, as well as therapeutic agents including dexamethasone and antisense oligodeoxyribonucleotides. However, drugs with very high molecular weight, such as vancomycin, show limited suitability for this technique. Overall, ocular iontophoresis represents a promising alternative approach for targeted ophthalmic drug delivery. [47]

Contact Lenses for Ocular Drug Delivery

Contact lenses are polymer-based devices placed on the cornea primarily to correct refractive errors. They may be fabricated from either hydrophilic or hydrophobic polymers and are generally classified as hard or soft lenses. Beyond vision correction, therapeutic contact lenses have emerged as a convenient platform for ocular drug delivery. Their ability to adhere to the moist ocular surface through surface tension allows drugs to remain in contact with eye tissues for longer periods. As a result, drug diffusion across the cornea increases while drug loss through the lacrimal drainage system decreases. Compared with conventional eye drops that require frequent administration, drug-loaded contact lenses can significantly improve drug bioavailability and reduce dosing frequency [48]. One common method for preparing drug-loaded lenses involves soaking the lenses in a drug solution so that the drug becomes incorporated into the polymer matrix. Drug-eluting contact lenses function as solid dosage forms that provide sustained drug release, ensuring prolonged drug residence on the corneal surface. This approach minimizes the overall drug dose required and decreases systemic absorption. In 2022, the first commercial drug-releasing contact lens, ACUVUE® Theravision® with Ketotifen, was introduced for the treatment of ocular allergy symptoms. [49] The mechanism of drug delivery involves diffusion of the drug into the tear film located behind the contact lens, followed by dispersion within the tear fluid and absorption through the cornea. Continuous drug uptake by the cornea maintains a lower drug concentration in the tear film compared with the lens, creating a concentration gradient known as the sink effect, which supports sustained drug release and stable therapeutic levels. Several studies highlight the potential of this technology. Wu et al. developed pirfenidone-loaded contact lenses using a PVA insert between silicone elastomer layers, which increased drug residence time in

tears and aqueous humor while using a much smaller drug dose than eye drops [108]. Ding et al. designed a contact lens containing microtubes for glaucoma therapy that allowed drug release for up to 45 days and responded to changes in intraocular pressure to regulate drug delivery [109]. Similarly, Xu et al. created a micelle-based contact lens carrying latanoprost and timolol, which successfully reduced intraocular pressure for more than a week [110]. In another study, Jiao and colleagues prepared an antimicrobial hydrogel contact lens incorporating quaternary ammonium chitosan and tannic acid, showing nearly complete antibacterial activity against Escherichia coli and Staphylococcus aureus while also reducing oxidative stress. [50]

Microneedles

Microneedles (MNs) represent a novel and minimally invasive strategy for ocular drug delivery. These tiny needle structures can penetrate only a few hundred micrometers into the sclera, enabling localized drug administration while minimizing damage to deeper ocular tissues. Compared with conventional approaches such as intravitreal injections, microneedles offer advantages including controlled drug release, targeted delivery, ease of administration, and relatively low manufacturing cost. They have shown particular potential in the treatment of posterior eye disorders such as diabetic retinopathy, age-related macular degeneration, and posterior uveitis [51]. By depositing drugs directly near the sclera, therapeutic agents can diffuse into deeper tissues such as the choroid and retina, thereby improving ocular bioavailability and reducing drug wastage. Various microneedle designs have been explored, including solid, hollow, dissolving, and polymer-coated systems. [52] Recent studies have demonstrated the therapeutic promise of microneedle-based ocular systems. For instance, dissolving microneedle patches composed of hyaluronic acid and polylactic acid have been investigated for treating fungal keratitis, a major cause of corneal blindness [53]. In experimental models, these patches temporarily penetrated the corneal epithelium and promoted rapid healing, showing greater therapeutic effectiveness than conventional eye drops. Similarly, pen-type microneedle devices have been developed to improve insertion precision and enable localized drug delivery within the corneal stroma. Dissolving polymeric microneedle arrays made from polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) have also been studied for protein delivery. These systems were able to encapsulate proteins without structural degradation and release more than 80% of the loaded cargo within 48 hours, demonstrating efficient drug delivery across scleral tissues. Despite these advantages, certain limitations still exist. Microneedle application may cause local irritation, inflammation, or infection at the insertion site, and prolonged placement on the eye can lead to patient discomfort. In addition, challenges such as limited drug-loading capacity, variability in drug release, and potential safety concerns must be carefully addressed. As a result, although microneedle technology is widely studied, microneedle-based ophthalmic formulations have not yet reached routine clinical use. Further research and optimization are necessary to improve their safety, efficacy, and patient acceptability for long-term ocular therapy. [54]

Hydrogels

Hydrogels are widely explored in ocular drug delivery because of their hydrophilic nature and three-dimensional polymer network, which allows them to retain large amounts of water. This property provides several advantages compared with conventional eye drop formulations. Hydrogels can increase the residence time of drugs on the ocular surface, enable sustained drug release, and allow the delivery of multiple therapeutic agents simultaneously. Unlike traditional eye drops that are rapidly removed from the eye due to blinking and tear drainage, hydrogels remain longer at the site of application, improving drug availability. [55] Hydrogels can be administered through different routes, including topical, intravitreal, and intracameral delivery. Their porous structure supports high drug loading and controlled release behavior. Recent research has focused on developing stimuli-responsive hydrogels that release drugs when exposed to specific triggers such as temperature, pH, or ions. For instance, a hydrogel system composed of cyclodextrins, hyaluronic acid, carrageenan, and gellan gum was designed to improve the ocular delivery of the antifungal drug econazole, demonstrating slower and more controlled drug release compared with conventional solutions. Similarly, a thermosensitive glycol-chitosan hydrogel containing levofloxacin showed improved ocular bioavailability and significantly prolonged drug retention on the corneal surface. [56]

Bispecific Antibodies

Bispecific antibodies (bsAbs) are engineered proteins capable of recognizing two different epitopes either on the same antigen or on two separate targets. This dual-binding ability provides broader therapeutic potential compared with traditional monoclonal antibodies. BsAbs are generally categorized into two groups based on whether they contain a fragment crystalliz-

able (Fc) region. The first category includes IgG-like bsAbs, which possess an Fc region and structural characteristics similar to conventional IgG antibodies. Examples include technologies such as knobs-into-holes (KiH), CrossMab, and DuoBody. These molecules typically have molecular weights close to 150 kDa and exhibit longer half-lives, improved serum stability, and effector functions. However, their larger size may limit tissue penetration and their production processes can be complex. [57] The second category consists of fragment-based or non-IgG-like bsAbs, which lack an Fc region. Examples include single-chain variable fragments (scFv), bispecific T-cell engagers (BiTEs), and diabodies. Because of their smaller size (approximately 25–110 kDa), these molecules generally demonstrate better tissue penetration and reduced immune activation. However, they often have shorter half-lives and lower stability in circulation. BsAbs can function through several mechanisms, such as linking immune effector cells to diseased cells, modulating multiple signaling pathways, mimicking enzymatic cofactors, or facilitating targeted delivery through piggyback mechanisms [58]. Currently, several bsAbs have been approved for clinical use, mainly in oncology. An example relevant to ophthalmology is faricimab (Vabysmo®), which targets both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A). By inhibiting these pathways, faricimab reduces inflammation, vascular leakage, and abnormal blood vessel formation. It is administered as an intravitreal injection and is used to treat conditions such as neovascular age-related macular degeneration, diabetic macular edema, and retinal vein occlusion. [59]

Gene Delivery

Over the past three decades, gene therapy has emerged as a promising strategy for treating several ocular diseases, including glaucoma. Researchers have explored gene-based approaches for many inherited retinal and optic nerve disorders such as X-linked retinoschisis, Usher syndrome, retinitis pigmentosa, choroideremia, Leber congenital amaurosis, achromatopsia, and Leber's hereditary optic neuropathy. In addition, gene therapy is being investigated for acquired retinal conditions like wet age-related macular degeneration (AMD), diabetic macular edema, and retinal vein occlusion. Different techniques are used to introduce genetic material into ocular cells [60]. Viral vectors such as adenoviruses and adeno-associated viruses (AAV) are commonly used because they provide efficient gene transfer. Adenoviral vectors can carry relatively large genetic sequences; however, their use in retinal therapy is limited due to rapid clearance caused by pre-existing immune responses. Non-viral delivery strategies, including electroporation, magnetofection, aptamer-based systems, gene guns, and other physical approaches, have also been explored. These methods often involve delivering naked nucleic acids such as plasmid DNA, siRNA, mRNA, or miRNA, although their stability in tissues can be limited due to rapid degradation. [61] A major milestone in ocular gene therapy was the approval of Luxturna™ (voretigene neparvovec) by the US FDA in 2017 for the treatment of Leber congenital amaurosis type 2. This therapy uses an AAV vector to deliver a functional RPE65 gene encoding the isomerohydrolase enzyme in patients carrying biallelic mutations. Gene therapies can be administered through intravitreal, subretinal, or suprachoroidal routes. While subretinal and suprachoroidal injections enable precise targeting of retinal tissues, they often require specialized surgical procedures such as vitrectomy. Suprachoroidal delivery is gaining attention because of its relatively simpler administration and its current clinical use in treatments like Xipere® (triamcinolone acetonide) for uveitis. RNA-based and gene-editing technologies are also being investigated for ocular therapy. For example, SYL040012, a small interfering RNA (siRNA) drug candidate, targets the β2-adrenergic receptor in the ciliary body to reduce intraocular pressure [62]. Studies in rabbits demonstrated about a 20% reduction in intraocular pressure lasting several days. Advanced genome-editing approaches such as CRISPR/Cas9 have also shown promise. Researchers have used this technology to target viral genomes in infections like herpes simplex keratitis and to correct mutations associated with glaucoma, including the MYOC gene mutation linked to elevated intraocular pressure. Gene-silencing approaches are also being explored for diseases involving abnormal blood vessel growth. For instance, the siRNA compound Sirna-027 (AGN211745) targets VEGFR-1 to suppress vascular endothelial growth factor signaling in wet AMD [63]. Experimental studies have shown that intravitreal or periocular administration of this molecule can persist in retinal tissues for several days, leading to reduced VEGFR-1 expression and inhibition of pathological neovascularization. [64]

One of the earliest long-acting ophthalmic implants approved by the U.S. Food and Drug Administration (FDA) was Vitrasert, a non-biodegradable intravitreal implant containing ganciclovir. It was developed for the management of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome. The device used polymers such as polyvinyl alcohol (PVA) and ethylene-vinyl acetate (EVA) to regulate drug release and was surgically placed through the pars

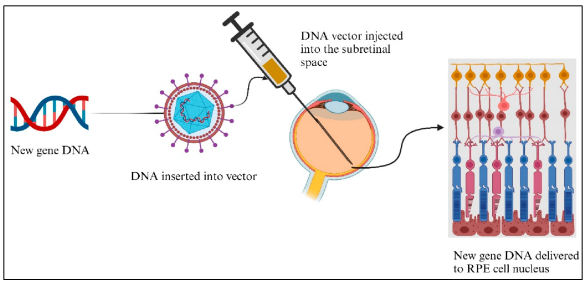

Figure 2. A schematic representation of subretinal gene therapy.

plana into the vitreous cavity [65]. Once implanted, it delivered ganciclovir at an approximate rate of 1 μg per hour for about five to eight months. Although the implant provided sustained antiviral therapy, its use was associated with several complications, including endophthalmitis, retinal detachment, and vitreous hemorrhage. In addition, the device required surgical replacement after the drug reservoir was depleted. [66] Following this development, additional non-biodegradable implants containing fluocinolone acetonide were introduced between 2005 and 2018 for the treatment of conditions such as noninfectious uveitis and diabetic macular edema (DME). These systems, also based on PVA-type polymers, were capable of maintaining drug release for much longer durations, in some cases up to three years. However, incorporating large biomolecules into non-biodegradable implants has proven difficult, which has encouraged the exploration of alternative delivery strategies. One promising approach is encapsulated cell technology (ECT), a cell-based delivery system designed for sustained intraocular therapy. In this method, genetically modified cells that produce therapeutic agents are enclosed within a semipermeable polymer capsule. The membrane allows nutrients, oxygen, and therapeutic proteins to diffuse outward while preventing immune cells from entering the capsule. The device is sealed at both ends and anchored near the pars plana, where it is attached to the sclera using a small titanium loop to maintain its position within the eye. [67] In recent years, biodegradable ocular implants have gained considerable attention because they can deliver drugs in a controlled manner while gradually degrading within the body. These systems are often used for conditions that require an initial high dose followed by a gradual decline in drug levels over periods ranging from a few days to several months. Biodegradable implants are commonly fabricated using polymers such as polylactic acid (PLA) and poly(lactic-co-glycolic acid) (PLGA). Drug release from these materials generally follows first-order kinetics, typically showing an initial burst release followed by a gradual decrease in drug concentration. By adjusting the ratio of PLA to PLGA, researchers can modify the degradation rate of the polymer and thereby tailor the duration of drug release, which may range from several weeks to many months. PLGA has been widely utilized in ocular implant design because it is biodegradable, biocompatible, and capable of sustaining drug delivery over extended periods [68]. Due to their relatively larger size and lower surface-to-volume ratio, these implants can often accommodate higher drug loads compared with smaller delivery systems. A well-known example of this technology is Ozurdex, a biodegradable implant that delivers dexamethasone for the treatment of macular edema. Approved by the FDA in 2009, this rod-shaped device contains 0.7 mg of dexamethasone embedded within a PLGA matrix. Using Allergan's NOVADUR delivery technology, the implant gradually breaks down into lactic and glycolic acid while continuously releasing dexamethasone in the vitreous cavity for up to six months. The implant is administered through an intravitreal injection, representing an important advancement in sustained ocular drug delivery. [69]

Advanced Pharmaceutical Approaches for Ocular Drug Delivery:

Additive Manufacturing Strategies in Ophthalmics

Conventional ocular drug delivery systems such as eye drops and oral medications have long been employed for the management of eye diseases. Although these approaches are clinically effective, they are often associated with several drawbacks, including poor patient adherence, rapid precorneal drug loss, low ocular bioavailability, and the inconvenience of repeated daily administration. In addition, the volume that can be retained in the conjunctival cul-de-sac is limited to nearly 30 μL, restricting the amount of drug that can be delivered through topical formulations. These challenges have encouraged the development of alternative ophthalmic drug delivery systems such as medicated contact lenses, ocular inserts, lacrimal plugs, intraocular implants, and biodegradable conjunctival devices designed to provide prolonged therapeutic action. [70] In recent years, three-dimensional (3D) printing technology has emerged as a promising platform for the fabrication of personalized ophthalmic devices and drug delivery systems. However, despite growing interest in this field, research involving the application of 3D printing for ocular therapeutics remains at a relatively early stage. [71] Three-dimensional printing, commonly known as additive manufacturing (AM), refers to the fabrication of objects through the sequential deposition of materials in a layer-by-layer manner using digital computer-aided design (CAD) models. Owing to its automated operation, design flexibility, and

ability to produce customized structures, this technology has gained considerable attention in pharmaceutical and biomedical applications. Personalized dosage forms and medical devices can be tailored according to the individual requirements of patients, thereby improving therapeutic outcomes and treatment efficiency. Furthermore, the compact and portable nature of 3D printing systems allows on-demand manufacturing at hospitals, pharmacies, remote healthcare settings, and even environments such as space missions. Another important advantage is its suitability for small-batch production during preclinical and clinical investigations, where frequent dose adjustments based on pharmacokinetic and pharmacodynamic responses may be required. Consequently, additive manufacturing has become an attractive strategy for developing advanced ophthalmic formulations and implantable ocular devices. [72]

Fused Filament-Based 3D Printing: Among the available 3D printing methods, material extrusion-based technologies have been widely explored for the preparation of ocular drug delivery systems and implantable devices. Depending on the feed material employed during the extrusion process, these techniques are categorized into fused deposition modeling (FDM), direct powder extrusion (DPE), and semi-solid extrusion (SSE), also referred to as bioprinting. Fused deposition modeling is one of the most extensively investigated approaches in pharmaceutical manufacturing. In this technique, thermoplastic polymeric filaments containing active pharmaceutical ingredients (APIs) are heated above their melting temperature and extruded through a nozzle onto a build platform according to a digitally programmed design. Layer-by-layer deposition enables the fabrication of complex geometries with high precision. Although FDM can generate intricate structures with relatively fine resolution, additional post-processing procedures such as support removal, polishing, and surface finishing are often necessary to improve the final appearance and quality of printed products. [73] FDM offers multiple advantages, including low equipment cost, rapid production, mechanical robustness of printed objects, and compatibility with numerous FDA-recognized Generally Regarded as Safe (GRAS) polymers. Drug incorporation into filaments can be achieved either through hot-melt extrusion (HME) or by soaking preformed filaments in drug solutions to permit passive diffusion of the API. Among these approaches, HME-assisted FDM is more frequently preferred because it ensures better drug distribution throughout the filament. Nevertheless, the elevated temperatures involved during processing may limit the application of this method for thermosensitive compounds. In contrast, passive diffusion methods generally result in lower drug-loading efficiency, restricting their use in formulations requiring higher doses. Topical treatment of glaucoma is frequently compromised by rapid tear turnover, blinking, nasolacrimal drainage, and limited corneal permeability, all of which reduce ocular drug retention. Injectable therapies, although effective, may cause discomfort and require administration by trained healthcare professionals. To overcome these limitations, researchers have explored 3D-printed ocular devices capable of sustained drug release. Mohamdeen and coworkers fabricated personalized contact lenses containing timolol maleate using a combination of HME and FDM techniques. Initially, the lenses exhibited a yellowish appearance due to thermal exposure during printing; however, transparent lenses were successfully obtained by operating below the melting temperature of the drug. The developed lenses sustained drug release for approximately seven days, although issues such as initial burst release and limited corneal permeability were still observed. [74] In another investigation, Wu and colleagues examined the influence of printing temperature conditions on the fabrication of polylactic acid (PLA)-based microneedle arrays coated with rhodamine B as a model compound. The researchers demonstrated that increasing the nozzle and stage temperatures improved interlayer bonding and reduced void formation within the printed structures, ultimately enhancing the mechanical properties of the microneedles. [75]

Semi-Solid Extrusion Printing Techniques: Unlike FDM, which utilizes solid filaments as feed material, semi-solid extrusion (SSE) printing employs gels, pastes, or hydrogel-based formulations. This technology has attracted considerable interest in drug delivery, tissue engineering, and bioprinting applications because it operates at relatively low temperatures and enables single-step manufacturing. In addition, the use of disposable syringes or cartridges may simplify regulatory compliance and reduce contamination risks. Since filament preparation is not required, SSE can improve manufacturing efficiency and formulation consistency. The increasing availability of biocompatible hydrogels and bio-inks has encouraged the investigation of SSE printing for ophthalmic applications. Tagami and colleagues developed levofloxacin-loaded ocular patches intended for antibacterial corneal therapy using hydrogel inks composed of hydroxypropyl methylcellulose (HPMC), mannitol, and xylitol. After printing and freeze-drying, the patches exhibited mucoadhesive behavior and formed hydrogels upon hydration, thereby prolonging ocular residence time and reducing drug

drainage. Similarly, Ioannou and coworkers fabricated biodegradable implants containing 5-fluorouracil (5-FU) for preventing conjunctival fibrosis following glaucoma surgery [76]. The implants were prepared using polycaprolactone and chitosan matrices loaded with 1% 5-FU. The developed system demonstrated favorable biocompatibility, biodegradability, and sustained drug release over an eight-week period, potentially reducing the need for repeated postoperative injections. Another study by Paleel and associates focused on intracameral implants containing high concentrations of timolol for glaucoma therapy. The SSE-fabricated implants achieved sustained drug release for nearly eight weeks without producing significant toxicity toward human trabecular meshwork cells. Collectively, these studies highlight the ability of SSE technology to create personalized and biocompatible ocular implants capable of improving treatment adherence and long-term therapeutic outcomes. [77]

Photopolymerization-Based 3D Printing Methods: Although FDM and SSE are commonly employed in pharmaceutical manufacturing, their application in ophthalmic formulations may be limited when producing highly intricate structures due to relatively large nozzle diameters and the requirement for extensive post-processing. To address these challenges, vat photopolymerization (VPP)-based techniques such as stereolithography (SLA) and digital light processing (DLP) have gained attention for ophthalmic device fabrication. These methods offer superior resolution, smoother surface characteristics, and thinner layer formation compared with extrusion-based technologies. In VPP systems, liquid photopolymerizable resin is selectively cured by light exposure in a layer-by-layer fashion to produce solid structures. SLA utilizes ultraviolet laser light to polymerize specific regions of the resin, whereas DLP projects an entire image layer simultaneously, enabling faster printing speeds. Since printing occurs under relatively mild thermal conditions, these methods are particularly suitable for thermolabile drugs and sensitive biomolecules [78]. SLA technology has been investigated for the fabrication of microneedle molds and ocular delivery systems. Fitaihi and coworkers designed cone-shaped microneedles with optimized aspect ratios for effective ocular tissue penetration. Their findings emphasized the significance of adjusting parameters such as orientation angle and layer thickness to achieve accurate and mechanically stable structures. In another study, SLA-generated molds were used to prepare dissolving microneedles composed of HPMC and polyvinylpyrrolidone (PVP K90). Among the materials employed in SLA and DLP systems, polyethylene glycol diacrylate (PEGDA) is one of the most widely used photopolymerizable agents because of its favorable biocompatibility. Xu and colleagues fabricated dexamethasone-loaded punctal plugs using DLP printing with PEGDA and PEG 400. Formulations containing PEG 400 exhibited drug release for approximately one week, whereas plugs composed solely of PEGDA sustained release for more than three weeks. These findings indicate the potential of DLP printing for producing personalized punctal plugs for dry eye management. [79] Goto and collaborators further explored DLP printing to fabricate azithromycin-loaded contact lenses using PEGDA-based formulations. The lenses demonstrated sustained drug release along with antimicrobial activity comparable to commercially available eye drops. Variations in the ratio of PEGDA to PEG 400 significantly influenced swelling behavior and release kinetics. In another notable study, researchers developed DLP-printed contact lenses integrated with nanoscale surface patterns generated by laser ablation. These modifications enabled the lenses to function as wearable biosensors for monitoring ocular parameters. Such advancements demonstrate the growing potential of DLP printing not only in sustained ocular drug delivery but also in the development of smart ophthalmic diagnostic systems. [80]

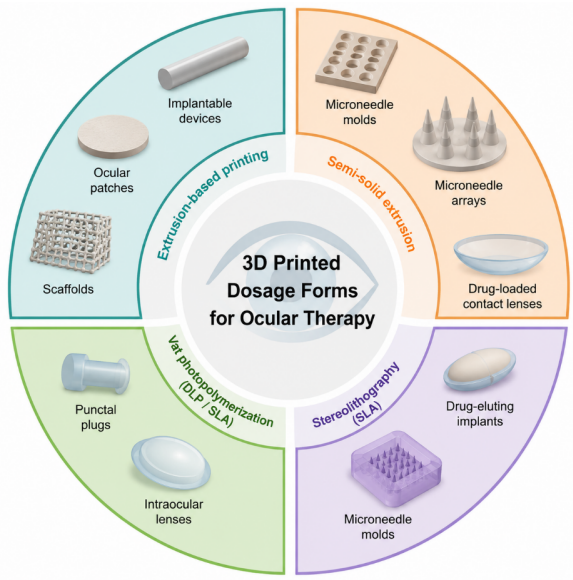

Figure 3. Applications of Three-Dimensional Printing Technologies in Ocular Drug Delivery Systems

Over the last several years, 3D printing has emerged as a promising technology in the field of personalized ocular therapy, particularly for retinal and corneal applications. Despite its growing importance, several technical and regulatory barriers continue to limit its broader implementation. Challenges associated with this technology include the limited availability of suitable pharmaceutical excipients, constraints related to

software and printing equipment, and concerns regarding the mechanical quality of the final printed products, such as inadequate strength, rough surface characteristics, and variability in performance. [81] Among the different 3D-printing approaches used for ocular formulations and drug-delivery devices, semi-solid extrusion (SSE) and vat photopolymerization (VPP) are commonly employed. However, the presence of residual solvents in many printed formulations remains a significant concern. In addition, the dependence on photopolymerizing and crosslinking agents, many of which have limited biocompatibility, further restricts the clinical applicability of these systems. Therefore, there is a critical need to develop novel excipients that are safe, biodegradable, biocompatible, environmentally sustainable, and suitable for ocular use. Another important limitation is that many currently available 3D printers are not fully compliant with Good Manufacturing Practice (GMP) standards, raising concerns regarding the safety, reproducibility, and quality of products intended for human use. High installation and operational costs associated with printers and raw materials also create economic challenges, particularly in healthcare settings where large-scale production may still offer greater cost efficiency. To improve product reliability and manufacturing consistency, non-destructive analytical approaches such as process analytical technologies (PATs) may be incorporated either during or after the printing process instead of relying solely on destructive testing methods. At the same time, robust quality-control systems must be implemented to ensure compliance with regulatory expectations and product safety standards. [82]

Hot-Melt Extrusion: Hot-melt extrusion (HME) is a pharmaceutical manufacturing technique originally adapted from the plastics industry. The process involves feeding drug(s) and excipient(s) into an extruder, where rotating screws apply heat and mechanical shear to melt, mix, and transport the materials. The molten mass is then pushed through a die, cooled, and collected as an extrudate. Processing is usually carried out at temperatures above the polymer glass transition temperature (Tg) or melting temperature (Tm). HME provides efficient molecular-level mixing between APIs and excipients, resulting in formulations with excellent content uniformity and improved product quality. The technology is widely used for developing oral, ocular, topical, and modified-release dosage forms. It is particularly valuable for enhancing the solubility and bioavailability of poorly water-soluble drugs by producing amorphous dispersions and co-crystal systems. The major advantages of HME include continuous manufacturing, solvent-free processing, scalability, automation, and high reproducibility. Screw configurations can also be customized to achieve the required mixing intensity for different formulations. In addition, HME can be integrated with advanced technologies such as 3D printing and monitored using process analytical tools like UV–VIS and NIR spectroscopy. However, heat-sensitive biomolecules such as proteins and peptides may not be suitable for this process, making preformulation studies essential before product development. [83]

Injection Molding: Injection molding is one of the most commonly employed fabrication methods in the medical device sector because it enables the production of highly precise and structurally complex systems with good manufacturing consistency. In ocular drug delivery, this technique has gained considerable importance for developing implantable devices capable of providing prolonged and controlled release of therapeutic agents. Both biodegradable and non-biodegradable polymeric implants can be prepared using this approach depending on the intended clinical application. During formulation development, several factors must be carefully optimized, including biocompatibility of the materials, preservation of drug integrity, and the desired drug release behavior. Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) are frequently selected due to their favorable safety profile and controlled degradation characteristics [84]. In addition, the selection of polymers, excipients, and drug incorporation strategies should be tailored to the ocular environment, which is characterized by specific physiological conditions such as pH variations, enzymatic activity, and rapid clearance mechanisms. Injection molding provides important advantages such as ease of large-scale production, reproducibility, and the ability to manufacture implants with uniform dimensions. Nevertheless, certain limitations remain associated with this process. Maintaining the stability of heat-sensitive drugs during manufacturing is particularly challenging because elevated processing temperatures may lead to degradation of the active compound. Therefore, parameters including molding temperature, injection pressure, and cooling conditions require careful optimization to maintain both drug stability and polymer integrity, as these factors directly influence the final release profile of the implant. Furthermore, the miniature size and sophisticated architecture of ocular implants make it difficult to achieve homogeneous drug distribution and precise dosing throughout the device. [86]

Table 3. Applications of 3D Printing Technologies in the Development of Ophthalmic Drug Delivery Systems and Ocular Devices

Device / Delivery System	Active Pharmaceutical Ingredient (Drug Loading)	Materials / Excipients Used	Printing Technique	Key Outcomes and Potential Applications
Drug-loaded contact lenses	Timolol maleate (1% w/w)	Ethylene vinyl acetate (EVA) and polylactic acid (PLA)	Hot-melt extrusion fused deposition modeling (HME-FDM)	The fabricated lenses demonstrated an initial rapid release phase followed by a controlled release pattern extending up to three days, indicating suitability for glaucoma therapy.
Microneedle systems	Rhodamine B (model compound)	Polylactic acid (PLA)	Fused deposition modeling (FDM)	The produced microneedles were found suitable for surface coating with therapeutic agents and may serve multiple biomedical and ocular delivery purposes.
Molds for dissolvable microneedles	Galantamine hydrobromide	PLA filaments along with PVA/PVP blends	Fused deposition modeling (FDM)	Customized molds fabricated through FDM technology enabled the preparation of drug-incorporated dissolving microneedles.
Ocular patches	Levofloxacin (0.5% w/w)	Hydroxypropyl methylcellulose (HPMC), mannitol, and xylitol	Semi-solid extrusion (SSE)	The patches exhibited antibacterial potential against ocular infections with the majority of drug release occurring within 1–2 hours.
Intracameral implants	Timolol maleate (5–10% w/w)	Polycaprolactone (PCL)	Semi-solid extrusion (SSE)	Long-acting implants were engineered to maintain sustained drug delivery for nearly eight weeks, offering potential benefits in glaucoma management.
Ocular implants	5-Fluorouracil (1% w/w)	Polycaprolactone and chitosan	Semi-solid extrusion (SSE)	The implant design aimed to minimize conjunctival scarring and fibrosis following glaucoma-related surgical procedures.
Hydrogel scaffolds	Betamethasone sodium phosphate (2.5% w/w)	Polyethyleneimine--based hydrogel	Semi-solid extrusion (SSE)	Bioprinted hydrogel scaffolds demonstrated promise for localized treatment of ocular inflammatory conditions.
Dissolving microneedles	Placebo formulation	Polyvinylpyrrolidone (PVP) and polyvinyl alcohol (PVA)	Stereolithography (SLA)	Prototype dissolvable microneedles were successfully produced as exploratory systems for ophthalmic drug delivery applications.
Molds for dissolvable microneedles	Placebo formulation	Polylactic acid (PLA)	Stereolithography (SLA)	SLA-fabricated molds were effectively utilized for manufacturing HPMC- and PVP K90-based dissolving microneedles.
Punctal plugs	Dexamethasone (10–20% w/w)	PEGDA and PEG 400	Digital light processing (DLP)	Formulations prepared entirely with PEGDA achieved prolonged corticosteroid release lasting beyond three weeks for dry eye management.

Antimicrobial contact lenses	Azithromycin (1% w/w)	PEGDA and PEG 400	Digital light processing (DLP)	The printed lenses displayed notable antimicrobial efficacy with inhibition zones comparable to marketed ophthalmic formulations.
Hollow microneedles	Placebo formulation	Commercial biocompatible resins	Digital light processing (DLP)	Angled-printing strategies produced hollow microneedles with improved structural geometry compared with flat-printed counterparts.
Device / Delivery System	Active Pharmaceutical Ingredient (Drug Loading)	Materials / Excipients Used	Printing Technique	Key Outcomes and Potential Applications

AI and Digital Technologies in Ophthalmic Drug Development

Emerging Role of AI in Eye Care Therapeutics

Ophthalmic drug development presents unique challenges because of the eye's specialized anatomy, complex physiological barriers, and distinct routes of drug administration. At the same time, advanced imaging techniques and digital biomarkers create opportunities for more precise therapeutic development. Artificial intelligence (AI) and digital healthcare technologies are increasingly transforming this field by accelerating drug discovery, improving prediction accuracy, and supporting precision medicine approaches for ocular diseases. [87]

AI-Based Target Discovery: Several ocular disorders, including age-related macular degeneration (AMD), glaucoma, cataracts, and corneal dystrophies, are linked to protein misfolding and abnormal cellular signaling. Understanding the three-dimensional structure of these proteins is essential for identifying therapeutic targets. Conventional techniques such as X-ray crystallography, nuclear magnetic resonance spectroscopy, and cryo-electron microscopy provide detailed structural information but are expensive, labor-intensive, and time-consuming. AI-driven computational tools have significantly improved this process. DeepMind's AlphaFold platform revolutionized protein structure prediction by accurately estimating protein conformations from amino acid sequences. The introduction of AlphaFold2 and AlphaFold3 further enhanced prediction accuracy and expanded capabilities to include interactions involving DNA, RNA, and small molecules. These developments have accelerated computer-aided drug design by rapidly identifying potential binding sites and reducing the cost and duration of early-stage drug discovery. AI-powered multi-omics platforms such as PandaOmics also support target identification by integrating transcriptomics, proteomics, and biomedical literature databases. These systems prioritize novel and druggable targets more efficiently than conventional approaches. Similar AI methodologies have been applied in peptide discovery from microbiome and extinct-organism datasets, opening new possibilities for antimicrobial therapies and peptide-based ocular treatments. [88]

CADD and Molecular Optimization: Once a therapeutic target is identified, computational drug design tools are used to predict how candidate molecules interact with biological systems. Structure-based drug design relies on the three-dimensional structure of target proteins, while ligand-based drug design focuses on the properties of previously known active compounds. AI-enhanced molecular docking enables rapid screening of millions of compounds by predicting binding affinity and interaction patterns with target proteins. This approach has shown potential in identifying therapies targeting vascular endothelial growth factor (VEGF), an important mediator in retinal diseases such as AMD. Molecular dynamics simulations further improve prediction accuracy by modeling the behavior of drugs and proteins in dynamic biological environments. Machine learning-based quantitative structure-activity relationship (QSAR) models are also widely used to predict therapeutic activity and optimize lead compounds. Recent deep learning approaches, including generative AI systems, can design entirely new molecules with desirable pharmacological properties. These technologies have significantly shortened the timeline for discovering novel antimicrobial peptides and may similarly accelerate ocular drug development. [89]

Explainable AI in Drug Discovery: One limitation of conventional AI systems is the lack of transparency in prediction mechanisms. Explainable AI (XAI) addresses this issue by improving the interpretability of AI-generated outputs. Techniques such as SHAP and LIME help researchers identify which molecular fea-

tures contribute most strongly to drug-target interactions. Platforms such as SmartCADD integrate AI with quantum mechanics-based approaches to improve virtual screening and predict drug absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles more accurately. Explainable models are especially valuable in ophthalmology because ocular diseases involve highly complex molecular pathways requiring reliable and interpretable predictions. [90]

Organoids and Organ-on-a-Chip Technologies: Traditional animal models often fail to fully replicate human ocular physiology and may raise ethical and translational concerns. As alternatives, organoids and organ-on-a-chip (OoC) systems have emerged as advanced preclinical platforms. Retinal organoids derived from stem cells can mimic the structure and function of human retinal tissue, while OoC systems recreate physiological microenvironments using microfluidic technology. [91] Recent retinal OoC models have successfully reproduced photoreceptor-retinal pigment epithelium interactions and choroidal neovascularization, enabling more realistic drug screening and toxicity evaluation. AI integration further enhances these systems by automating image analysis, optimizing experimental conditions, and processing large datasets generated from high-throughput screening platforms. Deep learning algorithms have also been applied for angiogenesis analysis, vessel segmentation, and phenotypic screening in retinal organoids. These technologies improve experimental reproducibility and may significantly accelerate the discovery of therapies for retinal disorders and ocular infections. [92]

AI in ADMET Prediction: Physiologically based pharmacokinetic (PBPK) modeling is increasingly used to predict the absorption, distribution, metabolism, and elimination of ophthalmic drugs. However, accurate ocular PBPK modeling is challenging because of the eye's complex anatomy, multiple delivery routes, and physiological barriers such as tear turnover, blinking, and corneal permeability. AI offers a promising solution by extracting meaningful physiological parameters from large datasets and developing adaptive nonparametric models capable of predicting complex drug behaviors. Machine learning systems can estimate corneal permeability, intraocular distribution, and ocular metabolism more accurately than traditional methods. Advanced neural network models, including Neural-ODE and long short-term memory (LSTM) architectures, are also being explored for optimizing treatment regimens and improving pharmacokinetic predictions. [93]

Translational Biomarkers and Precision Monitoring

Recent progress in high-throughput sequencing and single-cell technologies has transformed the understanding of how drugs interact with biological systems, creating new opportunities for precision therapeutics. These advances enable researchers to study molecular alterations in greater depth and support adaptive patient selection strategies during clinical trials. For example, whole-genome sequencing can classify patients according to genetic variations, helping clinicians tailor therapies more effectively and improve treatment outcomes. Unlike traditional pharmacogenomics, which mainly examines individual genetic mutations, artificial intelligence (AI) enables a broader systems-level evaluation of gene–gene and gene–environment interactions that influence therapeutic responses. [94] Growing interest in drug–omics associations has further improved the understanding of complex interactions between drugs and biomolecules. Ophthalmology is particularly suited for these approaches because the eye contains highly specific biomarkers, including proteins, nucleic acids, and metabolites found in tears, aqueous humor, and vitreous humor. Since these biomarkers are locally concentrated, they provide a clearer representation of the ocular microenvironment compared with systemic markers. Liquid biopsy techniques allow these biomarkers to be collected through minimally invasive procedures, offering real-time insights into disease progression and therapeutic response. For instance, complement-related molecules detected in aqueous humor have been strongly linked with age-related macular degeneration (AMD) and glaucoma, making them promising therapeutic targets. [95] Advances in computational biology have also encouraged the use of multi-omics approaches integrating epigenomic, transcriptomic, proteomic, lipidomic, and metabolomic data to better understand ocular diseases. Researchers have already developed transcriptomic and proteomic maps for healthy and diseased retinal tissues, including diabetic retinopathy models. AI-driven analytical systems can identify biological pathways associated with retinal aging and treatment response, opening new possibilities for targeted therapies. Proteomic biomarkers are also increasingly used to monitor therapeutic outcomes in conditions such as geographic atrophy. [96] One major challenge in omics-based research is the presence of confounding variables that obscure meaningful biological signals. AI-based frameworks such as context-aware deconfounding autoencoders (CODE-AE) help overcome this issue by separating genuine biomarkers from technical noise, batch effects, and patient variability. Such

approaches improve the prediction of patient-specific drug responses and strengthen the reliability of precision medicine models. Applying these technologies in ophthalmology could significantly enhance biomarker-guided diagnosis and therapeutic targeting. [97]

AI-Enhanced Ocular Imaging and Therapeutic Prediction

Imaging technologies play a central role in ophthalmic diagnosis and monitoring. Modalities such as color fundus photography, fluorescein angiography, optical coherence tomography (OCT), and OCT angiography generate detailed structural and functional information about the eye. Emerging imaging systems, including visible-light OCT, multispectral imaging, and fluorescence-based techniques, provide even deeper insights into retinal metabolism and physiology. AI algorithms greatly improve the interpretation of these imaging datasets by rapidly identifying disease-related features such as retinal thickness, vascular alterations, and structural abnormalities. These automated analyses reduce dependence on manual grading, improve consistency, and accelerate clinical decision-making. Recent advances in unsupervised learning and vision–language models have also enabled AI systems to identify subtle pathological patterns without requiring predefined labels. Such systems can recognize disease-associated morphological changes in conditions like AMD, sarcoidosis, and rare retinal disorders that may not be easily visible to clinicians. AI also supports treatment monitoring by detecting early structural changes and predicting therapeutic response. Biomarkers extracted from imaging data can help determine treatment frequency and identify patients most likely to benefit from specific interventions. Generative AI (GenAI) further contributes by simulating hypothetical post-treatment images, allowing clinicians and patients to visualize potential outcomes more effectively. These AI-derived metrics may eventually serve as secondary endpoints in clinical trials, supporting faster decision-making during drug development. In glaucoma research, for example, AI can evaluate retinal nerve fiber layer thickness and other neural structural changes rather than relying solely on intraocular pressure measurements. Such insights are particularly valuable for the development of neuroprotective therapies aimed at preserving retinal and optic nerve function. [98]

Smarter Clinical Trial Design and Execution

Patient recruitment and monitoring remain major limitations in conventional clinical trials, often contributing to high failure rates. Traditional recruitment methods based on electronic health records (EHRs) and manual screening can overlook eligible participants or include unsuitable candidates. AI-driven predictive analytics improves this process by analyzing large datasets that include clinical history, laboratory findings, imaging results, and lifestyle-related factors. This strategy, known as clinical trial enrichment, increases the likelihood of selecting appropriate participants. In ophthalmology, AI analysis of OCT scans has demonstrated improved accuracy in identifying eligible AMD trial participants compared with conventional EHR-based approaches alone. AI also facilitates decentralized clinical trials, allowing participants to contribute remotely rather than traveling to centralized research sites. This is especially beneficial for elderly patients affected by retinal diseases such as AMD and diabetic retinopathy. Another important advancement is federated learning, which enables multiple clinical centers to collaborate while maintaining patient privacy. Instead of transferring sensitive data, federated learning allows AI models to learn from distributed datasets, resulting in stronger and more diverse clinical evidence. [99] AI-supported adaptive clinical trials further improve efficiency by dynamically modifying study protocols according to interim findings. Unlike traditional fixed trial designs, adaptive systems can redirect resources toward more promising therapeutic strategies and discontinue ineffective interventions earlier. Automation of routine tasks such as adverse-event reporting, patient follow-up, and data management also reduces workload and operational costs. A real-world example is the “Vibe Up” study, an AI-driven decentralized trial evaluating digital interventions for psychological distress. Using adaptive algorithms, participant allocation changes in real time according to emerging evidence, improving efficiency while reducing sample size requirements. The introduction of AI-powered Digital Twins represents another transformative innovation. Digital Twins are virtual patient models created using real-world clinical, imaging, genomic, and biomarker data. These models can generate synthetic control groups, reducing the need for large placebo arms and minimizing ethical concerns associated with withholding treatment. Regulatory agencies such as the European Medicines Agency (EMA) have already acknowledged AI-supported statistical frameworks like prognostic covariate adjustment (PROCOVA), which improve trial efficiency while maintaining scientific rigor. Digital Twins could integrate multimodal imaging and molecular biomarkers to predict treatment response and disease progression. Applications are emerging in proliferative vitreoretinopathy and glaucoma, where virtual patient models may help optimize individualized treatment strategies and

reduce dependence on extensive in vivo testing. [100] Wearable devices and smartphone-based AI tools are also reshaping clinical monitoring by enabling continuous patient engagement and real-time data collection. AI-assisted mobile applications can support ocular disease monitoring, improve treatment adherence, and strengthen communication between patients and healthcare providers. Studies have already shown that AI-supported care models improve self-management and follow-up compliance in diabetic retinopathy patients.

AI-Guided Drug Repurposing in Ophthalmology

Developing a new drug is costly, time-intensive, and associated with high failure rates. Drug repurposing offers an attractive alternative by identifying new therapeutic applications for already approved medications. Since the safety profiles of these drugs are already established, repurposing reduces development risks, lowers costs, and accelerates clinical availability. The rise of big data and global data-sharing platforms has made AI increasingly valuable in identifying repurposing opportunities. Natural language processing (NLP) and deep learning algorithms can analyze enormous volumes of scientific literature, clinical trial data, and EHRs to uncover hidden therapeutic relationships. During the COVID-19 pandemic, AI systems identified remdesivir, originally developed for Ebola, as a potential antiviral therapy against SARS-CoV-2, demonstrating the practical value of AI-driven repurposing. Recent developments in GenAI and large language models (LLMs) have expanded these capabilities further. These models can process large amounts of unstructured biomedical information and detect non-obvious drug–disease associations. Researchers have already explored AI-guided repurposing strategies for neurological diseases such as Alzheimer's disease, and similar applications are expected to emerge rapidly in ophthalmology. [101]

Regulatory Challenges in Ophthalmic Drug Development

Topical and locally administered ophthalmic drug products are categorized by the United States Food and Drug Administration (FDA) as complex formulations because of the significant challenges involved in their chemistry, manufacturing, and control (CMC) processes compared with conventional dosage forms. Over the years, the FDA has actively supported research initiatives through grants and collaborative programs involving academic institutions and contract research organizations worldwide to address regulatory and scientific hurdles associated with complex generic ophthalmic products. These initiatives have focused on a variety of ophthalmic dosage forms, including emulsions, ointments, inserts, and implants. Outcomes from these collaborative efforts have contributed to scientific publications, strengthened the regulatory justification for abbreviated new drug applications (ANDAs) and new drug applications (NDAs), supported the revision and development of regulatory guidelines, and accelerated the approval pathway for complex generic ophthalmic products. Recently, the FDA introduced the draft guidance titled "Quality Considerations for Topical Ophthalmic Drug Products" in 2023. In parallel, several product-specific guidance documents have also been updated or released to provide more detailed recommendations for the formulation development, characterization, and evaluation of ophthalmic products. Therefore, reviewing both general and product-specific guidance documents is essential for developers to remain aligned with current regulatory expectations. [102] Despite considerable progress in ophthalmic product development, establishing reliable in vitro–in vivo correlations (IVIVCs) remains a major scientific challenge. The FDA's original IVIVC guidance, published in 1997 for extended-release oral formulations, laid the foundation for adapting IVIVC concepts to other dosage forms. Although regulatory agencies do not universally require IVIVC studies for submissions, establishing meaningful correlations can greatly benefit formulation optimization and product evaluation. Among the available approaches, Level A IVIVC, which represents a point-to-point relationship between in vitro release and in vivo performance, is considered the most informative and is generally preferred by regulatory authorities. However, generating Level A IVIVC models for ophthalmic systems is considerably more difficult than for conventional oral dosage forms due to the anatomical and physiological complexity of the eye. Successful IVIVC development depends on several critical factors, including the predictive capability of the in vitro release method, the relevance of pharmacokinetic profiles in different ocular tissues following administration, and the selection of appropriate modeling approaches such as numerical deconvolution or physiologically based pharmacokinetic (PBPK) models. Another limitation is the practical difficulty of measuring drug concentrations directly within various compartments of the human eye. Consequently, animal models, particularly rabbits, are frequently explored for developing preclinical IVIVC relationships despite known interspecies translational limitations. [103] Artificial intelligence (AI) is increasingly transforming drug discovery and development; however, its integration

into pharmaceutical research also introduces several scientific, ethical, and regulatory concerns. AI-driven systems require access to extensive datasets for model training, raising important questions regarding data privacy, security, and patient confidentiality. Sharing healthcare-related data across institutions or countries may increase the risk of unauthorized exposure of sensitive information. To address these concerns, compliance with regulations such as the Health Insurance Portability and Accountability Act (HIPAA) and the General Data Protection Regulation (GDPR) has become increasingly important. Federated learning has emerged as a promising strategy to improve data privacy while enabling collaborative AI model development. In this approach, data remain within their original institutions, while only model parameters are shared with a centralized server for aggregation and optimization. This decentralized training framework minimizes direct data exposure while still supporting the development of high-performing machine learning models. Federated learning has shown potential in advancing AI-assisted drug discovery platforms, including technologies such as AlphaFold and organ-on-chip systems. Regulatory agencies worldwide are actively attempting to adapt existing frameworks to the growing influence of AI in healthcare and pharmaceutical innovation. The FDA has reviewed numerous submissions involving AI-based methodologies and, in March 2024, introduced a risk-based framework emphasizing four major priorities: encouraging collaboration to protect public health, promoting harmonized standards and best practices, supporting innovation-friendly regulatory approaches, and advancing research for evaluating and monitoring AI performance. Similarly, organizations such as the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA) are working toward standardized protocols for AI and machine learning applications in drug development. Nevertheless, the rapid evolution of generative AI and large language models (LLMs) continues to challenge existing regulatory systems, which currently lack comprehensive provisions addressing unpredictable AI-generated outputs. Regulatory oversight may also need to expand toward AI-supported biomarker analysis in ocular fluids such as aqueous humor and vitreous humor to ensure ethical and scientifically reliable implementation. At present, there is no universally accepted international regulatory framework governing AI in drug discovery, highlighting the need for coordinated global standards and harmonized oversight strategies. Furthermore, although life-cycle management approaches for continuous post-market monitoring of AI systems have been proposed, practical implementation remains complex. [104] The increasing use of AI in pharmaceutical innovation has also generated debate regarding intellectual property rights and patent eligibility. In the United States, patent laws recognize inventions that represent a “new and useful process”; however, algorithms themselves are often regarded as abstract concepts and may not qualify for patent protection. Additional uncertainty arises from legislation such as the Patient Eligibility Restoration Act of 2023, which excludes mathematical formulas and mental processes from patentable subject matter [105]. Questions have also emerged concerning the originality and inventorship of AI-assisted discoveries. Current legal interpretations under the Federal Circuit require inventors to be natural persons, meaning AI systems cannot be listed as inventors on patent applications. Patent applications involving AI technologies may also encounter challenges related to enablement and written description requirements under Section 112, particularly when vague references to machine learning or neural networks are provided without adequate methodological detail. To reduce such issues, patent specifications should provide comprehensive, clear, and technically detailed descriptions that fully explain the invention and its operational methodology. [106]

Conclusion

The development of effective ophthalmic therapies continues to face significant scientific, technological, and regulatory challenges due to the complex anatomy and protective barriers of the eye. Conventional ocular dosage forms often fail to achieve adequate therapeutic concentrations, particularly in posterior segment diseases, highlighting the need for more advanced and targeted delivery approaches. Recent progress in ocular implants, nanoparticles, liposomes, hydrogels, microneedles, nanomicelles, iontophoresis, and in situ gelling systems demonstrates the growing potential of next-generation ophthalmic drug delivery technologies to improve bioavailability, prolong drug residence time, and reduce dosing frequency. In parallel, additive manufacturing techniques such as three-dimensional printing and hot-melt extrusion are opening new possibilities for personalized ocular therapies and patient-specific medical devices. Artificial intelligence has further accelerated innovation in ophthalmic drug discovery by enabling rapid target identification, molecular optimization, predictive modeling, and biomarker analysis. Emerging AI-driven tools, combined with digital healthcare technologies, may substantially reduce development timelines and improve therapeutic precision in ocular medicine. However, issues related

to manufacturing scalability, regulatory compliance, long-term safety, data privacy, and ethical concerns remain important obstacles to clinical translation. Future progress in ophthalmic therapeutics will depend on multidisciplinary collaboration among pharmaceutical scientists, clinicians, engineers, computational researchers, and regulatory authorities. Continued advancements in both drug delivery technologies and AI-driven pharmaceutical development are expected to transform the management of ocular diseases and improve global visual health outcomes.

Conflict of interest:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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