Nanomedicine for Ocular Drug Delivery: From Bench to Bedside—Recent Advances, Clinical Translation, Patents and Future Perspectives

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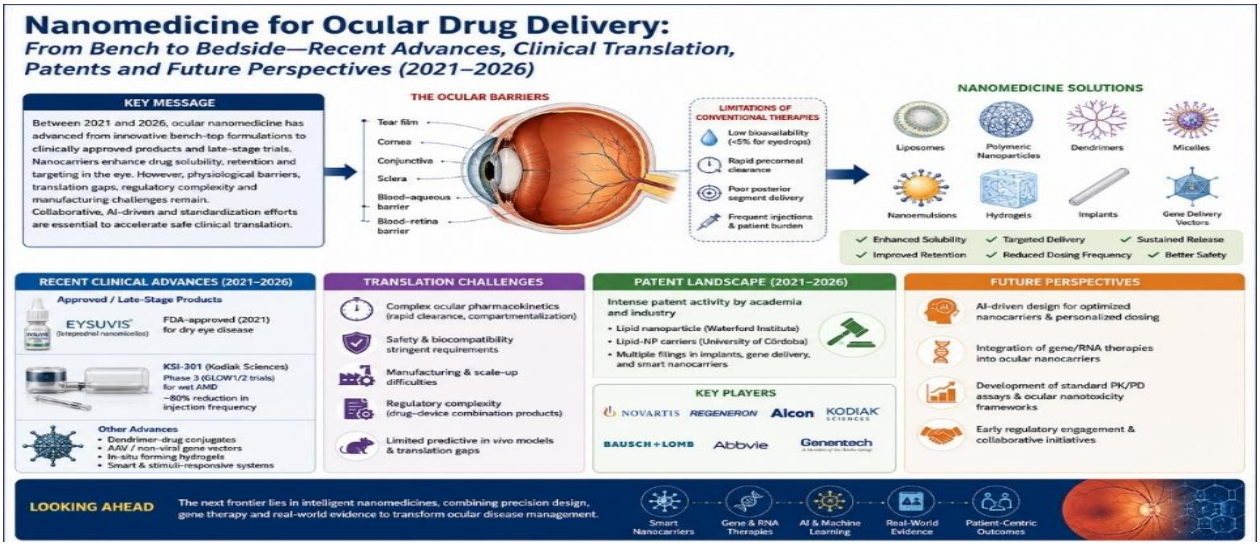
***Abstract*—Ocular nanomedicine has emerged as a promising strategy to overcome the eye's formidable barriers (tear film, cornea, blood–retina barrier) that limit conventional therapies. Recent years (2021–2026) have seen numerous new formulations—liposomes, polymeric nanoparticles (NPs), dendrimers, micelles, nanoemulsions, hydrogels, implants and gene-delivery vectors—designed to improve drug solubility, retention and targeting in the eye. Several products have been approved or advanced into late-stage trials: for example, the FDA-approved MPP-based eyedrop *Eysuvis* (loteprednol nanomicelles) for dry eye (2021), and late-phase trials of extended-release intravitreal agents (e.g. Kodiak's KSI-301) showing significantly fewer injections for wet AMD. At the same time, many innovative carriers (e.g. dendrimer-drug conjugates, AAV/nonviral gene vectors, and in-situ-forming hydrogels) have demonstrated encouraging preclinical efficacy for retinal diseases. Despite these advances, clinical translation remains challenging. Key hurdles include the eye's unique pharmacokinetics (rapid clearance, compartmentalization) and stringent safety requirements. Regulatory pathways are complex, as many ocular nanomedicines blur the line between drugs and devices (e.g. sustained-release implants). Manufacturing also poses scale-up difficulties, since nanoparticle properties (size, charge, drug-loading) can vary with even minor process changes. The patent landscape reflects intense activity (dozens of filings by academia and industry in 2021–2026) – key examples include Waterford Institute's lipid nanoparticle and University of Córdoba's lipid-NP carriers. Major gaps remain: there are few robust in vivo ocular models for human diseases, and many promising preclinical outcomes have failed to translate (e.g. some neuroprotective approaches) due to model mismatch. Regulatory guidelines are still evolving for nanomedicines; for instance, no unified standards exist for ocular nanotoxicity testing. Looking forward, integrating AI-driven design (for optimized nanoparticle formulations and personalized dosing) and gene/RNA therapies into ocular nanocarriers is a key frontier. Collaborative initiatives to define standard PK/PD assays, and early regulatory engagement, are recommended to accelerate safe translation. Below we review the recent literature in detail and provide recommendations for future development.**

***Index Terms*—Nanomedicine; Ocular drug delivery; Nanocarriers; Polymeric nanoparticles; Lipid-based nanoparticles; Nanoformulations; Retinal drug delivery; Corneal permeability; Blood–retinal barrier; Sustained drug release; Clinical translation; Regulatory challenges; Nanotoxicity; GMP manufacturing; Emerging ophthalmic therapies; Personalized medicine.**

Graphical Abstract



Schematic overview of the bench-to-bedside translation of nanomedicine for ocular drug delivery (2021–2026). The graphical abstract illustrates the major ocular barriers limiting conventional drug delivery, highlights advanced nanocarrier platforms—including liposomes, polymeric nanoparticles, dendrimers, micelles, Nano emulsions, hydrogels, implants, and gene-delivery vectors—and summarizes their therapeutic advantages in improving ocular bioavailability, targeted delivery, and sustained drug release. Recent clinical advances, translational challenges, patent activity, and future directions, including AI-assisted nanomedicine, gene/RNA therapeutics, and regulatory standardization, are integrated to provide a comprehensive perspective on the clinical translation of ocular nanomedicine.

I. INTRODUCTION

Ocular disorders, including dry eye disease (DED), glaucoma, age-related macular degeneration (AMD), diabetic retinopathy (DR), and other retinal degenerative conditions, represent a major global healthcare challenge and contribute substantially to visual impairment and blindness worldwide [1,2]. The eye possesses highly specialized anatomical and physiological barriers, including the tear film, corneal epithelium, conjunctival barrier, blood–aqueous barrier, vitreous matrix, and blood–retinal barrier (BRB), which collectively restrict effective drug penetration and distribution to ocular tissues [3,4]. Although conventional ophthalmic dosage forms such as eye drops, intravitreal injections, and implants remain the mainstay of therapy, their clinical effectiveness is frequently compromised by rapid precorneal elimination, limited ocular bioavailability (<5% of instilled dose for many topical formulations), frequent dosing requirements, invasive administration procedures, and poor patient compliance [5,6].Nanomedicine has emerged as an advanced drug delivery approach capable of overcoming several limitations associated with conventional ophthalmic formulations. Nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, polymeric micelles, nanoemulsions, lipid nanoparticles, hydrogels, and nanoscale implants, provide unique physicochemical advantages such as improved drug solubilization, protection of unstable therapeutic molecules, controlled and sustained drug release, enhanced tissue penetration, and potential site-specific targeting [7,8]. The nanoscale size and tunable surface characteristics of these systems enable interaction with ocular barriers and allow modification with functional ligands, mucoadhesive polymers, or mucus-penetrating coatings to improve precorneal residence time and enhance drug transport across ocular tissues [9]. Recent advances in ocular nanotechnology have demonstrated promising strategies for both anterior and posterior segment diseases. Mucoadhesive nanoparticles based on chitosan, hyaluronic acid, and other biocompatible

polymers have shown prolonged retention on the ocular surface, improving therapeutic outcomes in conditions such as dry eye, inflammation, and microbial keratitis [10]. Similarly, surface-engineered nanoparticles and ligand-functionalized nanocarriers have been investigated for enhanced delivery to retinal cells by overcoming vitreous diffusion limitations and improving accumulation within target tissues [11]. Furthermore, long-acting nanosystems, including biodegradable polymeric depots, lipid-based carriers, and nanoparticle-integrated implants, have demonstrated the potential to reduce administration frequency from daily dosing to weekly or monthly treatment regimens, which is particularly beneficial for chronic diseases such as AMD, glaucoma, and diabetic macular edema [12].The rapid evolution of nanomedicine has accelerated the transition of several ocular nanocarrier platforms from laboratory investigations toward clinical evaluation. Recent developments include nanomicelles formulations for anterior segment disorders, sustained-release biodegradable implants for glaucoma management, nanoparticle-based corticosteroid delivery systems, and emerging lipid/polymeric nanoparticles for nucleic acid and gene-based therapies [13,14]. However, despite significant progress, clinical translation remains challenging due to limitations associated with large-scale manufacturing, sterilization, long-term ocular safety, reproducibility, regulatory classification, and patient acceptance [15].This review provides a comprehensive overview of recent advances in ocular nanomedicine during the period **2021–2026**, focusing on nanocarrier engineering, mechanisms of ocular targeting, disease-specific applications, translational progress from preclinical studies to clinical trials, regulatory considerations, intellectual property development, and future perspectives. Different nanoplatforms, including liposomes, polymeric nanoparticles, dendrimers, micelles, nano emulsions, lipid nanoparticles, hydrogels, implantable systems, and nonviral gene delivery vectors, are critically evaluated according to their therapeutic potential in anterior and posterior segment disorders. By integrating recent scientific advancements with clinical translation and patent landscapes, this review aims to provide an evidence-based perspective on the future role of nanomedicine in transforming ocular drug delivery from bench research to bedside applications**.**

II. RECENT ADVANCES (2021–2026) BY NANOCARRIER TYPE AND THERAPEUTIC INDICATION

2.1 Liposomes

Liposomes are among the most extensively investigated nanocarrier systems for ocular drug delivery due to their excellent biocompatibility, structural versatility, and ability to encapsulate both hydrophilic and hydrophobic therapeutic molecules. These nanoscale vesicles typically consist of one or more phospholipid bilayers surrounding an aqueous core, with particle sizes generally ranging from 50–200 nm depending on composition and preparation methodology [16]. Hydrophilic drugs can be entrapped within the aqueous compartment, whereas lipophilic molecules are incorporated into the lipid bilayer, enabling delivery of a broad range of therapeutic agents including anti-inflammatory drugs, antimicrobial agents, corticosteroids, anti-vascular endothelial growth factor (anti-VEGF) molecules, peptides, and nucleic acids [17].Recent advances in liposomal ocular delivery have focused on improving drug retention, tissue penetration, and site-specific targeting. In anterior segment disorders, liposomal formulations have been investigated for enhancing corneal delivery of antibiotics, antifungal agents, immunomodulators, and anti-inflammatory drugs. For example, liposomal amphotericin B has demonstrated improved corneal retention and reduced toxicity compared with conventional formulations for fungal keratitis management [18]. Similarly, cyclosporine-loaded liposomes have been explored as an alternative approach for dry eye disease by improving aqueous solubility, epithelial penetration, and immunomodulatory activity [19].In posterior segment disorders, liposomes have attracted considerable attention because conventional topical administration provides limited retinal exposure due to anatomical barriers. Surface-modified liposomes, including cationic liposomes and ligand-functionalized systems, have demonstrated enhanced interaction with retinal cells and improved intracellular delivery. Recent preclinical studies have reported that modified liposomes can facilitate intravitreal delivery of anti-VEGF agents, nucleic

acids, and neuroprotective molecules for diseases such as AMD and diabetic retinopathy [20]. Glaucoma management represents another important application area for liposomal systems. Liposomal encapsulation of intraocular pressure (IOP)-lowering drugs such as latanoprost and brimonidine has been investigated to overcome rapid tear clearance and reduce the frequency of topical administration. These systems provide sustained drug release and improved corneal permeation compared with conventional eye drops, although clinical translation remains limited [21].

Advantages and Limitations

The major advantages of liposomes include their biological compatibility, biodegradability, ability to incorporate multiple therapeutic molecules, and capacity for surface modification. Their lipid composition allows interaction with biological membranes, which may improve corneal penetration and enhance drug bioavailability [22]. Furthermore, long-acting liposomal depots can provide prolonged drug release, potentially reducing dosing frequency and improving patient adherence. However, several challenges restrict widespread clinical application. Liposomes frequently suffer from physical instability, including aggregation, fusion, oxidation of phospholipids, and drug leakage during storage. Additionally, sterilization procedures and large-scale manufacturing remain technically challenging because minor variations in lipid composition can significantly influence particle characteristics and therapeutic performance [23]. Rapid clearance through tear drainage, mucociliary mechanisms, and immune-mediated uptake also limits ocular residence unless advanced surface modification strategies are applied.

Clinical Translation Status

Despite extensive preclinical research, liposome-based ophthalmic products remain relatively limited compared with other nanocarrier platforms. The liposomal formulation of verteporfin (Visudyne®) represents a successful clinical example for photodynamic therapy of choroidal neovascularization; however, it was developed before the 2021–2026 period [24]. During 2021–2026, most liposomal ocular systems remain in preclinical or early clinical development, particularly for retinal diseases, anti-VEGF delivery, gene therapy, and sustained anti-inflammatory treatment. The major barriers for clinical progression include long-term ocular safety assessment, reproducible manufacturing, and regulatory classification of nanomedicines [25].

2.2 Polymeric Nanoparticles and Nanospheres

Polymeric nanoparticles (PNPs) represent one of the most extensively studied nanotechnology platforms for ocular drug delivery because of their tunable physicochemical properties, biodegradability, and ability to provide controlled drug release. These systems are generally composed of biodegradable polymers including poly (lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA), polycaprolactone (PCL), chitosan, gelatin, and other natural or synthetic polymers [26]. Depending on the preparation method, polymeric nanoparticles can exist as nanospheres, where the drug is uniformly dispersed throughout the polymer matrix, or nanocapsules, where the drug is surrounded by a polymeric shell.Recent research between 2021 and 2026 has highlighted polymeric nanoparticles as promising carriers for both anterior and posterior segment disorders. In anterior ocular diseases, chitosan-based nanoparticles have received considerable attention because of their intrinsic mucoadhesive properties and ability to enhance corneal penetration. Chitosan nanoparticles loaded with antibiotics, corticosteroids, and anti-inflammatory agents have demonstrated prolonged ocular retention and improved therapeutic efficacy in models of keratitis and ocular inflammation [27]. For posterior segment diseases, PLGA and PLA nanoparticles have been widely explored for sustained delivery of corticosteroids, anti-VEGF agents, peptides, and nucleic acids. The biodegradable nature of PLGA enables gradual polymer erosion, allowing prolonged drug release within the vitreous cavity while reducing the frequency of intravitreal injections [28]. Surface modification strategies such as PEGylation, ligand attachment, and charge optimization have further improved nanoparticle diffusion through the vitreous matrix and enhanced retinal cellular uptake [29]. Polymeric nanoparticles are also being investigated for glaucoma therapy. Encapsulation of drugs such as latanoprost, timolol, and brimonidine within

biodegradable nanoparticles has shown potential for converting frequently administered topical therapies into sustained-release systems. These approaches may improve therapeutic compliance, particularly in patients requiring lifelong glaucoma treatment [30]. Furthermore, polymeric nanocarriers have emerged as effective platforms for advanced therapies involving proteins, peptides, and nucleic acids. Polymeric systems capable of delivering siRNA, mRNA, and gene-editing components are currently being evaluated for retinal disorders due to their potential advantages over viral vectors, including lower immunogenicity and improved repeat-dose capability [31].

Advantages and Limitations

Polymeric nanoparticles provide several advantages, including controlled drug release, high drug-loading capacity, protection of unstable molecules, and flexibility in modifying particle size and surface properties. Their degradation rate can be precisely controlled by altering polymer composition, molecular weight, and polymer-to-drug ratio, allowing customization according to therapeutic requirements [32].Nevertheless, polymeric nanoparticles face several translational challenges. PLGA degradation generates acidic by-products that may alter local ocular pH and potentially induce inflammatory responses if not appropriately controlled [33]. In addition, maintaining batch-to-batch reproducibility, achieving sterile manufacturing, controlling particle aggregation, and ensuring long-term ocular compatibility remain major regulatory concerns. Nanoparticles larger than approximately 200 nm may exhibit limited diffusion through the vitreous due to steric hindrance and interaction with extracellular matrix components [34].

Clinical Translation Status

Although polymeric nanoparticles have demonstrated significant success in experimental models, relatively few systems have reached advanced clinical development. A notable example is **KSI-301**, an antibody–polymer conjugate developed by Kodiak Sciences, which utilizes a phosphorylcholine-based polymer technology designed to extend intraocular residence time of anti-VEGF therapy for neovascular AMD. Clinical studies demonstrated the potential for extended dosing intervals compared with conventional anti-VEGF treatments, although later-stage outcomes highlighted the complexity of translating prolonged-release systems into clinical practice [35]. Another important example is **OCS-01**, a dexamethasone-based ocular formulation utilizing nanoparticle technology developed for diabetic macular edema. The formulation progressed to late-stage clinical evaluation, demonstrating the growing interest in nanoparticle-based corticosteroid delivery; however, clinical outcomes emphasized the need for optimized formulation design and patient selection [36]. Biodegradable polymer implants also represent an advanced form of polymer-based ocular delivery. Durysta® (bimatoprost implant)**,** a biodegradable intracameral implant based on polymer technology, received FDA approval in 2020 for reducing intraocular pressure in glaucoma patients and continues to demonstrate the clinical feasibility of long-acting polymeric ocular systems [37]. Overall, polymeric nanoparticles remain one of the most promising nanotechnology platforms for ocular drug delivery. Future progress will depend on improving manufacturing scalability, establishing long-term safety profiles, and developing targeted systems capable of achieving precise delivery to specific ocular tissues.

2.3 Dendrimers

Dendrimers represent a unique class of highly ordered, three-dimensional nanocarriers characterized by a symmetrical, branched molecular architecture. These nanosystems generally possess diameters between 5 and 20 nm and are composed of repetitive branching units that generate multiple surface functional groups capable of drug conjugation, encapsulation, or interaction with biological targets [38]. Among various dendrimers, polyamidoamine (PAMAM), polyester dendrimers, and poly(propylene imine) (PPI) derivatives have been extensively investigated for ocular applications due to their precise molecular structure, nanoscale size, and multifunctional surface chemistry [39].Recent advances in ocular dendrimer research have particularly focused on retinal targeting and neuroprotective applications. Unlike conventional nanoparticles that mainly rely on passive diffusion, dendrimers can exploit disease-associated cellular changes to achieve preferential accumulation.

Hydroxyl-terminated PAMAM dendrimers have demonstrated selective uptake by activated microglia and Müller glial cells in models of retinal inflammation and degeneration [40]. This intrinsic targeting capability has enabled dendrimers to deliver therapeutic molecules such as N-acetylcysteine, corticosteroids, and anti-inflammatory agents directly to pathological retinal cells. For retinal inflammatory diseases, dendrimer-based delivery systems have shown significant potential due to their ability to penetrate ocular tissues after intravitreal or systemic administration. Polyhydroxylated dendrimers containing anti-inflammatory drugs have demonstrated reduction of inflammatory cytokine expression and retinal tissue protection in experimental models of age-related macular degeneration (AMD), diabetic retinopathy (DR), and uveitis [41]. Furthermore, their small size facilitates movement through extracellular spaces, allowing improved distribution within retinal layers compared with larger particulate systems. Dendrimers are also being explored as nonviral gene delivery platforms. Their multiple surface amine or hydroxyl groups enable complex formation with nucleic acids such as DNA, siRNA, and mRNA. Surface modification with polyethylene glycol (PEG), peptides, or targeting ligands has been investigated to improve cellular uptake while reducing toxicity [42]. Such systems may provide future opportunities for treating inherited retinal disorders and retinal neurodegenerative diseases.

Advantages and Limitations

The major advantage of dendrimers is their highly controlled molecular architecture, which provides reproducible size, surface functionality, and pharmacokinetic behavior. Their multivalent structure allows simultaneous attachment of multiple therapeutic molecules or targeting ligands, improving intracellular delivery and therapeutic efficiency [43]. In addition, dendrimers can enhance the aqueous solubility of poorly soluble drugs by forming drug–dendrimer complexes or micelle-like structures. Despite these advantages, several limitations restrict clinical translation. High-generation dendrimers, particularly those containing positively charged amino groups, may induce cytotoxicity, membrane disruption, and inflammatory responses. Surface neutralization through hydroxyl modification or PEGylation is therefore required to improve biological compatibility [44]. Furthermore, complex synthesis procedures, purification requirements, high production costs, and regulatory challenges remain important barriers for large-scale manufacturing.

Clinical Translation Status

Compared with liposomes and polymeric nanoparticles, dendrimer-based ocular products remain primarily in the experimental stage. No dendrimer-based ophthalmic drug has received FDA approval to date. However, encouraging clinical progress has been observed with hydroxyl-terminated PAMAM dendrimer platforms. Ashvattha Therapeutics has developed hydroxyl PAMAM dendrimer-based drug delivery systems designed to target activated immune cells involved in ocular inflammation. Early clinical investigations have explored dendrimer–N-acetylcysteine conjugates for retinal disorders, including glaucoma-associated neuroinflammation [45]. Although these approaches are still under evaluation, they represent an important step toward disease-targeted nanomedicine. Overall, dendrimers provide a highly sophisticated platform for precision ocular therapy; however, successful translation will require optimization of safety, manufacturing scalability, and long-term ocular compatibility.

2.4 Polymeric Micelles

Polymeric micelles are self-assembled nanostructures formed from amphiphilic block copolymers containing hydrophilic and hydrophobic segments. These systems typically range from 5–100 nm and possess a hydrophobic core capable of solubilizing poorly water-soluble drugs, surrounded by a hydrophilic shell that provides aqueous stability [46]. Common polymers used for ocular micellar formulations include PEG–PLA, PEG–PCL, Soluplus®, and other FDA-compatible amphiphilic materials. Due to their small size and excellent solubilization capacity, polymeric micelles have emerged as promising carriers for anterior segment diseases. Many ophthalmic drugs, including cyclosporine A, corticosteroids, and immunomodulators, exhibit poor aqueous solubility, limiting their effectiveness in conventional eye drops. Micellar systems overcome this limitation by increasing apparent drug solubility and improving

drug transport across the corneal epithelium [47]. A major advancement in ocular micelle technology is the development of mucus-penetrating delivery systems. PEGylated micelles reduce interaction with mucins, allowing improved movement through the tear film and enhanced drug availability on the ocular surface. This approach has been particularly valuable for chronic diseases such as dry eye disease, where rapid tear clearance significantly reduces conventional drug exposure [48]. Clinically available examples include Cequa®, a nanomicellar cyclosporine A ophthalmic formulation developed using NCELL™ technology, which improves cyclosporine solubility and ocular penetration for dry eye treatment [49]. Similarly, Eysuvis® (loteprednol etabonate ophthalmic suspension 0.25%) utilizes advanced delivery technology to improve corticosteroid availability for short-term treatment of dry eye flare symptoms [50].

Advantages and Limitations

Polymeric micelles offer several advantages, including enhanced solubility of hydrophobic drugs, improved corneal penetration, small particle size, and patient-friendly topical administration. Their aqueous stability allows incorporation into conventional ophthalmic dosage forms without the discomfort associated with larger particulate systems [51]. However, micelles have limitations related to drug loading capacity and structural stability. Dilution after administration into the tear fluid may destabilize micellar structures, resulting in premature drug precipitation. Additionally, maintaining long-term physical stability during storage remains challenging. Regulatory evaluation of nanomicellar systems also requires extensive characterization because small changes in composition may alter biological performance [52].

Clinical Translation Status

Polymeric micelles represent one of the most clinically advanced ocular nanotechnology platforms, particularly for anterior segment disorders. Several nanomicellar and nano solubilization-based products have reached commercialization, demonstrating successful translation of nanotechnology into ophthalmic therapy. Future applications are expected to expand toward posterior segment delivery, including retinal inflammation, AMD, and diabetic macular edema. However, achieving effective retinal penetration through topical administration remains a major challenge, and most posterior segment micellar systems are currently in preclinical development.

III. MECHANISMS OF OCULAR DRUG DELIVERY WITH NANOCARRIERS

The therapeutic effectiveness of ophthalmic formulations is primarily limited by the complex anatomical and physiological barriers of the eye, including tear turnover, corneal epithelial tight junctions, conjunctival clearance, vitreous diffusion restrictions, and the blood–retinal barrier (BRB). Nanocarrier-based drug delivery systems overcome these challenges through multiple complementary mechanisms, including enhanced barrier penetration, controlled release, targeted delivery, improved ocular retention, and optimization of physicochemical properties. These mechanisms enable increased drug concentration at the site of action while reducing systemic exposure and dosing frequency [53].

3.1 Barrier Penetration and Enhanced Tissue Transport

One of the major advantages of nanocarriers is their ability to improve penetration across ocular barriers by optimizing particle size, surface chemistry, and hydrophilicity. The corneal epithelium represents the primary barrier for topical drug administration due to its multilayered structure and tight junctions that restrict molecular transport. Nanoparticles generally exhibit improved epithelial interaction compared with conventional drug molecules because of their nanoscale dimensions and modifiable surfaces [54]. Particle size plays a crucial role in ocular penetration. Nanocarriers within the range of approximately 20–200 nm demonstrate improved diffusion through ocular tissues compared with larger particles because they experience reduced steric hindrance. Smaller nanoparticles can penetrate superficial ocular barriers more efficiently, whereas particles exceeding several hundred nanometers may exhibit restricted movement due to extracellular matrix interactions and rapid clearance [55]. Surface modification further enhances penetration efficiency. Hydrophilic coatings such as polyethylene glycol (PEG) reduce nonspecific interactions with tear proteins and mucins, producing mucus-penetrating nanoparticles capable of reaching

the epithelial surface. In contrast, positively charged nanocarriers, including cationic liposomes and chitosan nanoparticles, interact electrostatically with negatively charged mucin glycoproteins, resulting in prolonged residence time on the ocular surface [56]. For posterior segment delivery, nanoparticle size and surface characteristics influence diffusion through the vitreous humor. Nanocarriers with optimized dimensions and neutral or slightly negative surface charge demonstrate improved mobility through the vitreous matrix, facilitating delivery toward retinal tissues following intravitreal administration [57].

3.2 Sustained Release and Depot Effect

A major objective of ocular nanomedicine is to achieve prolonged therapeutic exposure while reducing the frequency of administration. Conventional ophthalmic solutions are rapidly removed due to tear drainage, blinking, and nasolacrimal clearance, resulting in extremely short residence times after topical administration. Nanocarriers overcome this limitation by functioning as drug reservoirs capable of gradual and controlled release [58]. Biodegradable polymeric nanoparticles composed of materials such as poly (lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and chitosan provide sustained release through controlled polymer degradation and drug diffusion mechanisms. Similarly, lipid nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and hydrogel-based systems have demonstrated prolonged drug retention in ocular tissues [59]. Long-acting delivery is particularly important for posterior segment diseases such as AMD, diabetic macular edema, and retinal vascular disorders, where repeated intravitreal injections are associated with patient burden and potential complications. Polymer-based anti-VEGF delivery platforms have demonstrated extended intraocular exposure, reducing treatment frequency compared with conventional monoclonal antibody injections [60]. A notable example is the antibody–polymer conjugate technology used in **KSI-301**, which was designed to extend intraocular retention of anti-VEGF therapy by increasing molecular size and reducing clearance from the vitreous cavity. Although clinical outcomes demonstrated the complexity of achieving prolonged efficacy across diverse patient populations, this platform represents an important advancement toward long-acting retinal therapies [61].

3.3 Targeting and Bioadhesion

Nanocarriers provide opportunities for active and passive targeting of specific ocular tissues through surface modification and biological interactions. Passive targeting depends on physicochemical properties such as size, charge, and hydrophobicity, whereas active targeting involves attachment of ligands including antibodies, peptides, aptamers, or carbohydrates that recognize specific cellular receptors [62]. Dendrimer-based systems represent an important example of targeted ocular delivery. Hydroxyl-terminated PAMAM dendrimers have demonstrated preferential accumulation within activated microglia and macrophages associated with retinal inflammation. This disease-associated uptake enables selective delivery of anti-inflammatory agents while minimizing exposure to healthy retinal cells [63]. Ligand-functionalized nanoparticles have also been investigated for retinal targeting. Peptides containing arginine–glycine–aspartic acid (RGD) sequences can interact with integrin receptors overexpressed on angiogenic endothelial cells, providing a potential strategy for targeted delivery of anti-angiogenic drugs in neovascular AMD [64]. Similarly, targeting ligands directed toward retinal pigment epithelial (RPE) cells have been explored for improving intracellular delivery in retinal degeneration. Bioadhesion represents another important mechanism, particularly for anterior segment delivery. Natural polymers such as chitosan, hyaluronic acid, and alginate enhance ocular retention by forming interactions with mucin layers, thereby increasing contact time between the formulation and corneal epithelium [65].

3.4 Reduction of Ocular Clearance and Protection of Therapeutic Molecules

Rapid elimination from the ocular surface remains one of the major limitations of topical ophthalmic therapy. Approximately most of the administered dose from conventional eye drops is removed through blinking, tear secretion, and nasolacrimal drainage. Nanocarriers improve ocular retention by reducing clearance and enhancing interaction with biological barriers [66].

Mucus-penetrating nanoparticles, particularly PEG-coated systems, are designed to move through the mucin network without becoming trapped, allowing enhanced access to epithelial surfaces. Conversely, mucoadhesive nanoparticles increase retention by forming temporary interactions with mucus layers [67]. In addition to improving retention, nanocarriers protect sensitive therapeutic molecules from degradation. Proteins, peptides, RNA molecules, and gene-editing components are highly susceptible to enzymatic degradation within ocular fluids. Encapsulation within lipid nanoparticles, polymeric nanoparticles, or dendrimers provides physical protection and maintains biological activity until reaching the target site [68]. For intravitreal delivery, nanoparticle size optimization is critical because particles must remain sufficiently mobile within the vitreous while avoiding rapid elimination. Nanocarriers below approximately 500 nm generally demonstrate improved distribution within the vitreous environment, although optimal size depends strongly on surface charge, composition, and disease condition [69].

3.5 Influence of Physicochemical Properties on Ocular Performance

The therapeutic performance of ocular nanocarriers is strongly influenced by physicochemical parameters including particle size, morphology, surface charge, hydrophobicity, and mechanical properties. These characteristics determine diffusion behavior, cellular uptake, drug loading capacity, and biological interactions. Small nanoparticles (approximately 5–20 nm), such as dendrimers, can diffuse through dense extracellular matrices more efficiently, whereas larger nanoparticles may provide prolonged retention due to slower mobility. However, excessively small particles may undergo rapid elimination or insufficient drug loading, highlighting the importance of balancing size and therapeutic requirements [70]. Surface charge also significantly influences ocular behavior. Positively charged nanoparticles generally exhibit enhanced cellular interaction and mucoadhesion, but excessive positive charge may increase toxicity and inflammatory responses. Neutral or mildly charged systems often demonstrate improved tolerability and prolonged circulation within ocular compartments [71]. Particle morphology has recently gained attention as an additional design parameter. Non-spherical nanoparticles, including nanorods and elongated particles, exhibit different diffusion patterns and cellular interactions compared with conventional spherical nanoparticles. Although still primarily experimental, shape-engineered nanocarriers may provide future opportunities for directional transport within ocular tissues [72].

Conclusion of Mechanistic Strategies

Overall, nanocarriers improve ocular drug delivery by integrating multiple mechanisms, including enhanced barrier penetration, prolonged retention, targeted cellular uptake, controlled drug release, and protection of unstable therapeutic molecules. The combination of rational particle engineering with biological targeting approaches has enabled the development of next-generation ocular therapies capable of addressing previously unresolved challenges in anterior and posterior segment drug delivery. Future advances will depend on integrating artificial intelligence-based formulation optimization, biomimetic surface engineering, and clinically scalable manufacturing strategies to achieve precise and personalized ocular nanomedicine.

IV. PRECLINICAL AND CLINICAL TRANSLATION OF OCULAR NANOMEDICINES

The successful development of ocular nanomedicines requires a systematic translational pathway involving comprehensive in vitro characterization, advanced ex vivo evaluation, relevant animal models, and carefully designed clinical studies. Although nanocarriers have demonstrated remarkable potential in improving ocular bioavailability and therapeutic efficacy, successful clinical translation depends on establishing reliable correlations between physicochemical characteristics, biological interactions, pharmacokinetic behavior, and therapeutic outcomes [73].

4.1 Preclinical Models and Outcomes

In Vitro Evaluation

In vitro models represent the initial stage of ocular nanomedicine development and are commonly employed to evaluate cytotoxicity, cellular uptake, permeability, drug release behavior, and molecular mechanisms of action. Human corneal epithelial cell

models such as HCE-T cells, primary corneal epithelial cultures, and retinal pigment epithelial models such as ARPE-19 cells are frequently used for preliminary screening of ocular nanocarriers [74]. These cellular models provide valuable information regarding nanoparticle internalization, intracellular trafficking, inflammatory responses, and cellular compatibility. For example, fluorescence-labelled polymeric nanoparticles and liposomal systems have been widely evaluated using retinal pigment epithelial cells to understand uptake mechanisms and potential applications in AMD and diabetic retinopathy therapy [75]. However, conventional two-dimensional cell cultures do not fully reproduce the complex ocular microenvironment, including tear dynamics, extracellular matrix interactions, immune responses, and multilayer tissue organization. Therefore, results obtained from these models require validation using more advanced biological systems.

Ex Vivo Ocular Models

Ex vivo models using isolated ocular tissues provide an intermediate platform between cell-based studies and animal experiments. Excised corneal tissues from bovine, porcine, or rabbit sources are commonly used to investigate drug diffusion, tissue penetration, and retention characteristics of nanocarrier formulations [76]. For example, nanoparticle-based corticosteroid formulations have demonstrated enhanced corneal permeation and prolonged tissue retention compared with conventional drug solutions in ex vivo corneal models. These studies provide important information regarding formulation performance and help optimize particle size, surface charge, and polymer composition before in vivo evaluation. Despite their advantages, ex vivo systems lack physiological processes such as tear secretion, blinking, immune activity, and ocular metabolism, limiting their ability to completely predict clinical performance.

Three-Dimensional Organoids and Advanced Models

Three-dimensional (3D) ocular organoids represent an emerging technology for improving prediction of nanomedicine behavior. Retinal and corneal organoids derived from stem cells can reproduce important structural and cellular features of native ocular tissues, including photoreceptors, retinal neurons, and supporting epithelial layers [77]. These models provide opportunities for evaluating nanoparticle penetration, toxicity, and therapeutic effects under more physiologically relevant conditions. Although currently limited by high cost, technical complexity, and lack of standardization, organoid-based approaches are expected to become valuable tools for personalized ocular drug development.

In Vivo Animal Models

Animal studies remain essential for evaluating ocular pharmacokinetics, biodistribution, toxicity, and therapeutic efficacy. Commonly used models include mice, rats, rabbits, and larger animals such as pigs and non-human primates.

Different disease-specific models are employed depending on therapeutic objectives:

- Laser-induced choroidal neovascularization (CNV) models are widely used for evaluating AMD therapies**.**
- Streptozotocin-induced diabetic models are used for diabetic retinopathy studies.
- Elevated intraocular pressure (IOP) models are used for glaucoma research.
- Experimental autoimmune uveitis models evaluate anti-inflammatory nanotherapies.

Nanocarrier-based anti-VEGF delivery systems have demonstrated promising outcomes in AMD models by reducing pathological angiogenesis and improving retinal drug retention compared with free drug administration [78]. Similarly, sustained-release polymeric nanoparticles and lipid-based carriers have produced prolonged intraocular drug exposure and improved therapeutic effects in glaucoma and inflammatory eye disease models [79].

Challenges Associated with Preclinical Translation

Despite encouraging results, significant differences exist between experimental models and human ocular physiology. Species variations in ocular size, vitreous composition, immune response, retinal structure, and drug metabolism can influence nanocarrier performance after clinical translation [80]. Several nanomedicine approaches showing strong efficacy in rodent models have failed to demonstrate equivalent benefits in human trials. This challenge is particularly evident in retinal neuroprotection strategies, where improvement in animal biomarkers does not always

correspond with clinically meaningful visual improvement. Therefore, selection of appropriate disease models, incorporation of clinically relevant endpoints, and validation in larger animal models are critical for improving translation success. Although primate models provide greater physiological similarity to humans, their use is restricted by ethical considerations, cost, and regulatory requirements.

4.2 Clinical Trials and Translational Outcomes (2021–2026)

The period between 2021 and 2026 has witnessed increasing clinical interest in ocular nanomedicine, particularly for sustained drug delivery, anterior segment inflammation, and retinal vascular disorders. However, clinical outcomes have demonstrated both successful translation and significant challenges.

KSI-301 (Tarcocimab Tedromer): Long-Acting Anti-VEGF Platform

Kodiak Sciences developed KSI-301 (tarcocimab tedromer), an antibody–biopolymer conjugate designed to increase molecular size and prolong intraocular retention of anti-VEGF therapy. The phosphorylcholine-based polymer technology was developed to extend dosing intervals compared with conventional anti-VEGF antibodies.

Early clinical studies demonstrated promising durability, with a proportion of patients maintaining disease control with extended treatment intervals. However, later-stage Phase III studies highlighted the complexity of achieving consistent superiority over existing anti-VEGF therapies across different retinal disease populations [81].

Although KSI-301 was not a conventional nanoparticle system, it represents an important example of nanotechnology-inspired molecular engineering for long-acting ocular therapy.

OCS-01: Nanoparticle-Based Dexamethasone Delivery

OCS-01 developed by Ocumension Therapeutics is a dexamethasone ophthalmic formulation based on cyclodextrin nanoparticle technology designed to improve corticosteroid solubility and ocular penetration.

Clinical studies demonstrated improved drug exposure and reduction of retinal thickness parameters in diabetic macular edema patients. However, later Phase III evaluation did not demonstrate statistically significant improvement in visual acuity compared with control treatment [82].

The outcome of OCS-01 emphasizes an important translational principle: improvement in pharmacokinetic parameters or anatomical biomarkers does not always guarantee clinically meaningful visual benefits.

Brimonidine Drug Delivery System (Brimo-DDS)

Sustained-release brimonidine delivery systems have been investigated for neuroprotection in retinal diseases including geographic atrophy associated with dry AMD. Brimo-DDS was designed as a biodegradable implant capable of prolonged brimonidine release.

Although preclinical studies demonstrated retinal neuroprotective effects, clinical evaluation showed limited efficacy in slowing geographic atrophy progression [83]. This highlights the difficulty of translating neuroprotective effects observed in experimental models into measurable clinical outcomes.

Nanomicellar and Mucus-Penetrating Eye Drops

Anterior segment nanomedicines have demonstrated comparatively greater clinical success.

Eysuvis® (loteprednol etabonate ophthalmic suspension 0.25%), developed using advanced drug delivery technology, received FDA approval for short-term treatment of dry eye disease exacerbations. Clinical studies demonstrated rapid reduction of ocular inflammation with acceptable safety profiles [84].

Similarly, Cequa® (cyclosporine ophthalmic solution 0.09%), based on nanomicellar technology, improved cyclosporine solubilization and ocular delivery for chronic dry eye disease management. Clinical studies demonstrated increased tear production and improved ocular surface parameters [85].

These examples demonstrate that nanotechnology has achieved faster clinical translation in anterior segment diseases compared with posterior segment disorders.

Gene Therapy and Nonviral Nanocarrier Translation

Gene-based therapies represent one of the most rapidly developing areas of ocular medicine. Although viral vectors such as adeno-associated virus (AAV) currently dominate clinical retinal gene

therapy, nonviral nanocarriers including lipid nanoparticles (LNPs) and polymeric nanoparticles are emerging because of their potential advantages in repeat dosing, manufacturing scalability, and reduced immunogenicity [86].

Recent advances in systemic LNP-mRNA technologies have accelerated interest in ocular applications. Several companies are investigating nanoparticle-based delivery of therapeutic RNA molecules targeting VEGF signaling and retinal degeneration pathways. However, most ocular LNP gene therapies remain in early clinical development, with Phase I/II studies evaluating safety and feasibility.

Overall Clinical Translation Perspective

The clinical development of ocular nanomedicine demonstrates a clear distinction between anterior segment and posterior segment applications.

- Anterior segment nanomedicines have achieved greater clinical success due to easier administration, direct accessibility, and lower biological complexity.
- Posterior segment nanomedicines face greater challenges due to vitreous diffusion limitations, retinal barriers, immune responses, and demanding clinical endpoints.

Successful products such as Cequa® and Eysuvis® validate the feasibility of nanotechnology-based ophthalmic therapy, whereas mixed outcomes from advanced retinal programs emphasize the need for improved predictive models and patient-specific approaches.

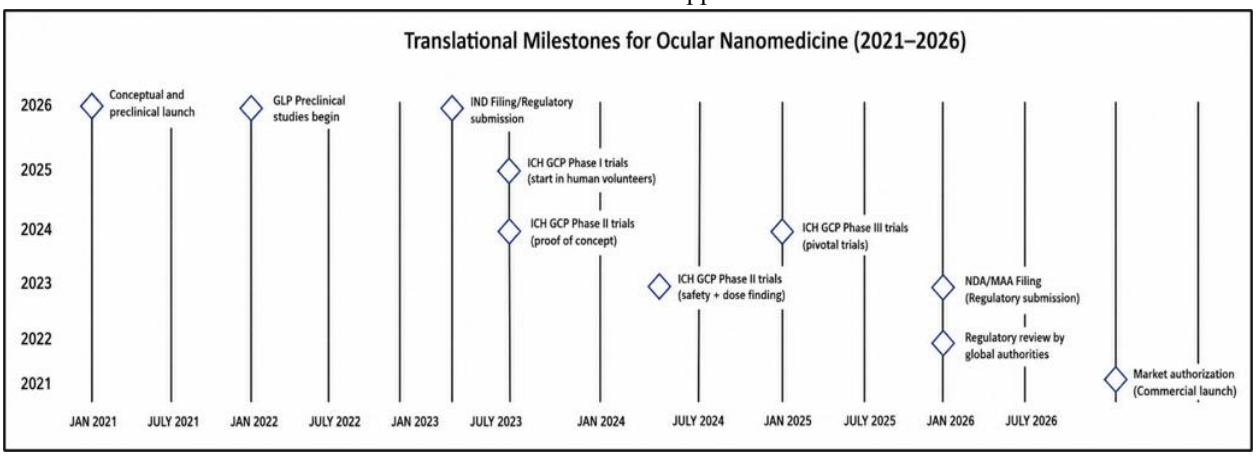


Figure 1. Chart: Ocular Nanomedicine Trials (2021–2025)

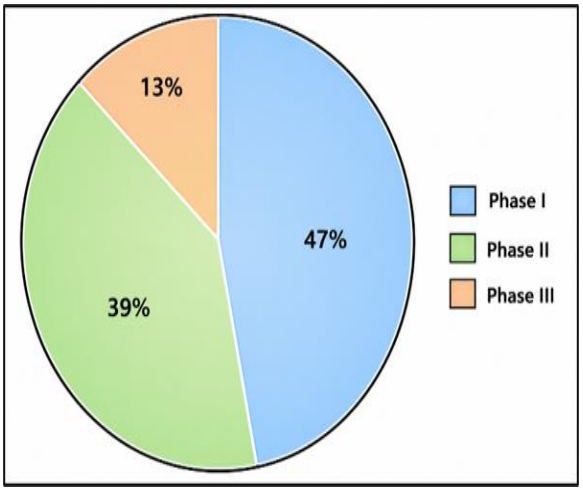


Figure 2. Distribution of Ocular Nanomedicine Clinical Trials by Development Phase (2021–2026)

5.1 Regulatory Pathways

Nanomedicines for ocular applications face complex regulatory considerations, requiring evaluation as drug products, medical devices, or combination products depending on their primary mode of action. Regulatory pathways involve extensive preclinical evaluation, investigational applications, and phased clinical trials before marketing authorization.

The unique physicochemical characteristics of nanoparticles, including particle size, morphology, surface charge, and composition, influence ocular biodistribution, pharmacokinetics, and potential toxicity. Therefore, regulatory agencies emphasize comprehensive characterization, ocular tolerance studies, biodistribution assessment, and long-term safety evaluation.

5.2 Safety, Efficacy and Manufacturing

Ocular safety remains a critical regulatory requirement for nanomedicine development. Toxicological evaluation includes ocular irritation studies, intraocular pressure monitoring, retinal histopathological assessment, electrophysiological analysis, and systemic toxicity evaluation following ocular administration.

Clinical efficacy assessment requires validated endpoints such as visual acuity, intraocular pressure reduction, optical coherence tomography (OCT) parameters, and disease-specific biomarkers. The relationship between nanoparticle pharmacokinetics, residence time, and therapeutic outcomes must be demonstrated during clinical development.

Manufacturing challenges mainly arise from maintaining nanoparticle reproducibility, sterility, scalability, and control of critical quality attributes (CQAs), including particle size distribution, zeta potential, drug loading, encapsulation efficiency, and batch-to-batch consistency.

Advanced manufacturing approaches such as microfluidics, high-pressure homogenization, and optimized lyophilization strategies are increasingly explored to improve scalability and stability of ocular nanomedicines.

VI. PATENT LANDSCAPE (2021–2026)

The patent landscape for ocular nanomedicine has grown markedly. Key patents (2021–2026) include:

- US20210085618A1/US11779543B2 (2021/2023) – *Waterford Institute of Technology (Ireland)*: Nanostructured lipid carriers (NLC) for ocular delivery of drugs. This covers solid-shell/liquid-core NPs (cholesterol and MCT lipids) showing increased corneal residence and controlled release. Granted as US11779543B2 in Oct 2023.
- WO2024102798A1 (2024) – *Universidad Nacional de Córdoba (Spain)*: Lipid nanoparticle carriers for ophthalmic, dermatologic and cosmetic actives. The invention relates to lipid nanocarriers for active ocular ingredients, indicating academic interest in multi-application lipid nanomedicine.
- WO2025144421A1 (2025) – *Chinese Inventors (Pat. CN113813388)*: Aqueous nanomicelle formulation containing difluprednate for ocular inflammation. This application (published mid-2025) teaches multi-surfactant micellar drops with <20 nm micelles for post-op inflammation, reflecting attempts to improve upon Durezol®.
- US20240207195A1 (2024) – *Waterford Inst.*: Continuation on ocular drug delivery systems (likely related to the 2021 NLC patent). Pending application covers methods and compositions for eye delivery (title "Ocular drug delivery").
- US20240307306A1 (2024) – *Waterford Inst.*: "Microemulsion for ophthalmic drug delivery". Likely a related family, focusing on emulsions for the eye (GB and EP equivalents exist).
- GB201721832A (2018 priority) – *Waterford Inst.* (UK grants in 2022): early PCT (WO2019123420A1) for ocular drug delivery, possibly predating above US filings. (Shows WIT's persistent patenting in this area.)
- InMed Pharmaceuticals (Canada/US) – Multiple patents granted 2024 on cannabinoid-based ocular formulations (e.g. INM-089 for dry AMD). While no US number is given in press releases, the patents cover novel cannabinoid derivatives delivered ophthalmically (trade press), highlighting interest in new drug classes and nanocarrier use for them.
- Other notable filings: A flurry of international patents (US, EP, CN, JP) by pharmaceutical companies and universities cover nanocarrier compositions. For instance, patents on dendrimer–oligonucleotide conjugates, PEGylated lipids, targeted liposomes, and polymeric micelle formulations have been filed. (A Controlled Release Society Patent Watch in late 2022 summarized 20+ new ocular DDS patents, many nanotechnology-based.)

Table 2 (below) lists representative patents with numbers, year, assignees, and links:

Patent (Number)	Year Pub.	Assignee/Inventor	Title
US20210085618A1 / US11779543B2	2021/2023	Waterford Inst. of Tech (Ireland)	Nanostructured lipid carrier for ocular delivery

Patent (Number)	Year Pub.	Assignee/Inventor	Title
WO2024102798A1	2024	Univ. of Córdoba (Spain)	Lipid nanoparticles as carriers (ocular)
WO2025144421A1	2025	(CN Inventors)	Ophthalmic difluprednate nanomicelles (gel)
US20240307306A1	2024	Waterford Inst.	Ophthalmic microemulsion composition
US20240207195A1	2024	Waterford Inst.	Ocular drug delivery (continuation)
(numerous others)	2021–26	Pharma & acad.	Liposomal, NP, dendrimer, gene-VLP patents (see text)

These patents indicate active IP in nanocarriers. In sum, dozens of new patents were filed worldwide in 2021–26 related to ocular delivery systems, reflecting rapid innovation.

VII. GAPS AND UNMET CHALLENGES

Despite advances, several critical gaps hinder progress:

- Translational Model Gap: Animal models often do not fully recapitulate human ocular diseases. For example, anti-VEGF in AMD: laser-induced choroidal neovascularization in rats is acute and resolves, unlike chronic human AMD. Nanocarrier behavior (distribution, clearance) can differ markedly between species, leading to "no effect" in human trials even when animals did well.
- Safety/Toxicology Standards: No consensus on ocular nanotoxicity protocols exists. Regulators emphasize it, but academia lacks standardized assays for chronic low-level toxicity (e.g. subtle retinal glial changes). This uncertainty slows approval. We note calls for validated 3D retinal models or microsurgical microfluidic "eye-on-a-chip" systems to better predict toxicity.
- Manufacturing Reproducibility: Many lab-scale formulations fail to scale. For example, an optimized NP recipe may yield 100 nm particles at bench, but 200 nm at pilot scale. Without deep characterization (e.g. single-particle tracking), unknown batch variability can arise.
- Economic and Clinical Adoption: Ocular drug development is expensive and small-volume. Companies must justify the cost of GMP nanomanufacturing vs. the niche market (e.g. a rare ocular disease). Investors are cautious without clear clinical success (the failure of some trials has chilled the space). Clinicians are also wary of adopting complex new delivery methods without long-term safety data.
- Regulatory Uncertainty: As noted, unclear frameworks (e.g. how to classify "nanocarrier" versus "drug") create uncertainty. Some products may be split-regulated (eye drop = drug, but an inserted implant coated with NP may be device+drug). Navigating this without similar precedents can delay development.
- Patient Recruitment and Endpoints: Many ophthalmic trials struggle with patient heterogeneity (e.g. dry eye severity) and placebo effects. Nanocarrier trials must carefully stratify patients; otherwise, modest benefits may be masked (as is often seen in dry eye studies).

In summary, successful translation will require filling these gaps with better models, clear regulatory roadmaps, advanced manufacturing platforms, and interdisciplinary collaboration between engineers, biologists, clinicians and regulators.

VIII. FUTURE PERSPECTIVES AND RECOMMENDATIONS

To accelerate bench-to-bedside progress in ocular nanomedicine, we suggest:

- Integrate AI and Data-Driven Design: Leverage artificial intelligence to optimize nanoparticle formulations and predict PK/PD. For example, machine learning can screen millions of polymer structures for those with ideal ocular properties (bioadhesion, permeability). Digital "eye models" could predict how changes in size/charge affect distribution. The integration of AI-driven design and digital monitoring can personalize treatments (e.g. adjusting dosing intervals based on patient-specific biomarkers of response).

- Focus on Combination Therapies: Many ocular diseases are multifactorial (inflammation + angiogenesis, etc.). Combining nanocarriers (e.g. dual-loaded NPs with steroid + anti-VEGF) could address multiple pathways. Also, pairing gene therapy vectors (e.g. AAV) with nanoparticle carriers (to re-dose or target non-viral gene editing) is promising.
- Advanced Preclinical Models: Develop organ-on-chip or humanized ocular models. 3D retinal organoids co-cultured with microglia could better assess nanoparticle effects on human retina. Ex vivo human corneal rings (from donor eyes) are underused for permeability testing.
- Regulatory Alignment and Guidance: We recommend closer dialogue between drug developers and regulators. Agencies should publish specific guidance on ocular nanomedicines (parallel to existing liposome/gene therapy guidances). Early submission of pre-IND data for feedback is advised. Harmonizing standards (e.g. OECD-like tests for ocular nanotoxicity) would benefit the field globally.
- Scalable Manufacturing Platforms: Invest in manufacturing innovations, such as microfluidic NP synthesis or modular "nanofactories" (continuous production lines). These could ensure consistent particle size and facilitate GMP compliance. Collaboration with existing biologics manufacturers might spread the cost of shared nanoformulation capabilities.
- Patient-Centric Trials: Use real-world evidence and digital monitoring (home OCT, vision self-tests) to augment trial data. Adaptive trial designs can allow quicker go/no-go decisions for novel carriers.
- Target Novel Indications: Beyond AMD/DR, nanomedicine could benefit currently untreatable conditions: e.g. delivery of CRISPR-Cas9 via NPs for inherited retinal dystrophies, or ocular vaccines via intranasal NP delivery. Proactive research into these areas should be encouraged.
- Public-Private Partnerships: Given the risks and costs, consortia (like NIH-funded NanoProMed) can de-risk early-stage research, creating pre-competitive data on ocular nano-PK and toxicity.

In summary, advancing ocular nanomedicine will require technical innovation (AI-driven design, new materials), improved translation models, and regulatory clarity. By addressing the gaps noted and pursuing the above strategies, the field can move closer to realizing the long-anticipated benefits of nanotechnology for eye care.

Table 1. Comparison of Key Nanocarriers for Ocular Delivery

Carrier	Composition	Size Range	Payloads (Examples)	Target Tissue	Advantages	Limitations	Clinical Status	Representative Sources
Liposomes	Phospholipid bilayers (~100–200 nm)	~50–500 nm (multilamellar)	Hydrophobic (e.g. latanoprost, steroids), hydrophilic (proteins in core)	Anterior (cornea), Posterior (retina via injection)	Biocompatible; can carry diverse cargo; fuse with cell membranes	Stability issues; rapid clearance if unmodified; scale-up (sterilization)	Preclinical/trials (few marketed)	General review
Polymeric NPs	Biodegradable polymers (e.g. PLGA, chitosan)	50–500 nm	Small drugs, biologics (bevacizumab, dexametha	Vitreous, retina (intravitreal); cornea (drops)	Tunable release (weeks–months); robust payload;	Acidic degradation byproducts; size sensitivit	Phase II/III (e.g. KSI-301); Durysta implant (FDA-	KSI-301 study.

Carrier	Composition	Size Range	Payloads (Examples)	Target Tissue	Advantages	Limitations	Clinical Status	Representative Sources
			sone)		PEGylation improves vitreous diffusion	y; manufacturing consistency	approved 2020)	
Dendrimers	Branched polymers (PAMAM, OH-PAMAM)	~5–20 nm	Drugs or dyes (neuroprotectants, steroids)	Retina/Müller cells (via intravitreal)	Precise size/charge; high drug-loading; cell targeting (ligand-free)	Costly synthesis; potential toxicity at high load; limited clinical data	Early-phase; some trials (glaucoma drug, etc.)	Dendrimer review
Micelles (Blk Copolymers)	Amphiphilic block copolymers (PEG–PLA, etc.)	~5–100 nm (core-shell)	Lipophilic drugs (loteprednol, cyclosporine)	Ocular surface (cornea/conjunctiva)	Huge solubility gain; small size penetrates mucus; comfortable drops	Stability (may dissociate), lower payload, regulatory novelty	Marketed (Eysuvis, Cequa); others in trials	Eysuvis launch
Hydrogels/Implants	Crosslinked polymers (HA, poloxamer; PLGA rods)	Macro (>100 µm) or microparticle gels	Drugs diffused (anti-VEGF proteins, steroids)	Cornea (drops/contact lens), vitreous (injectable implant)	Dramatic retention; sustained release over weeks–months	Vision interference; surgical insertion; limited payload	Some approved (Durysta implant); many in develo	Review
Gene Vectors (Nonviral)	Lipid NPs, cationic polymers, exosomes	~50–150 nm	DNA/RNA, siRNA, CRISPR components	Retina (subretinal or suprachoroidal); potentially cornea	Avoid viral immunogenicity; can re-dose; large payloads (mRNA)	Lower transfection than viruses; stability; ocular barriers	Early-stage (Phase I/II mRNA trials)	Preclinical review

Table 1 sources: Key nanocarrier attributes are summarized from recent reviews and clinical case studies. Clinical status is as of 2026.

Table 2. Selected Ocular Nanomedicine Patents (2021–2026)

Patent (Publication)	Year	Applicant/Inventor	Title/Focus	Link (Google Patents)
US20210085618A1 / US11779543B2	2021/2023	Waterford Institute of Technology (Ireland)	Nanostructured lipid carrier (NLC) for ocular delivery	US20210085618A1
WO2024102798A1	2024	Universidad Nacional de Córdoba (Spain)	Lipid nanoparticles as carriers for ophthalmic applications	WO2024102798A1
WO2025144421A1	2025	(China)	Nanomicelle formulation of difluprednate for post-op inflammation	WO2025144421A1
US20240307306A1	2024	Waterford Institute of Tech.	Ophthalmic microemulsion composition	US20240307306A1
US20240207195A1	2024	Waterford Institute of Tech.	Continuation: Ocular drug delivery methods	US20240207195A1
(Also cited:) GB201721832D0	2018	Waterford Institute of Tech.	Ocular drug delivery (basis of above family)	GB201721832D0

Table 2 sources: Patent data compiled from Google Patents and company press releases (e.g. InMed).

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