Recent advances in nanomedicine for ocular drug delivery

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ABSTRACT

Vision impairment is a major global health challenge, with its prevalence projected to rise significantly in the coming decades due to an aging population and increasing rates of chronic diseases. Ocular conditions such as age-related macular degeneration, cataracts, refractive errors, glaucoma, and diabetic retinopathy are among the primary causes of vision loss, collectively affecting nearly 200 million individuals worldwide. This growing burden has intensified the demand for ophthalmic therapies that are more effective, safer, and more targeted. Among existing treatment strategies, ocular drug delivery systems provide a non-invasive route for administering medications directly to ocular tissues. However, their clinical effectiveness is often compromised by various anatomical and physiological barriers, including tear turnover, blinking, nasolacrimal drainage, and blood-ocular barriers, which limit drug retention time and significantly reduce bioavailability. In response to these challenges, the application of nanomedicine has emerged as a highly promising strategy to improve ocular drug delivery. This review presents recent advances in drug nanodelivery systems – such as dendrimers, liposomes, nanoemulsion, solid lipid nanoparticles, *in situ* gel formulations, exosomes, metal-organic frameworks, and nanocrystals – that have demonstrated advantages in enhancing drug solubility, prolonging drug release, improving corneal penetration, and reducing dosing frequency and systemic side effects. In addition, the integration of artificial intelligence (AI) and personalized medicine in the development and optimization of ocular nanomedicine is explored. AI tools such as predictive modeling, machine learning algorithms, and data-driven formulation strategies remain underutilized in ophthalmology, yet they offer tremendous potential to accelerate innovation, individualize treatment, and enhance clinical translation. This review concludes that future research should prioritize not only the advancement of safer and more efficient drug nanodelivery systems but also the incorporation of AI to transform ocular drug delivery into a more precise and patient-centered approach.

Keywords:
Eye drops; nanocarrier; nanoparticle; nanotechnology; ocular drug delivery

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1. Introduction

Vision is widely regarded as the most vital sensory modality as it plays an integral role in our daily lives, making vision impairment caused by eye diseases particularly impactful and debilitating. According to the World Health Organization database, an estimated 2.2 billion people suffer from near or distance vision impairment, of which 1 billion cases could have been prevented with appropriate intervention.[1] Among these preventable cases, cataracts account for 94 million, uncorrected refractive errors for 88 million, and age-related macular degeneration, glaucoma, and diabetic retinopathy for 8 million, 7 million, and 4 million cases, respectively. Globally, the prevalence of ocular diseases has been observed to increase as the population grows. In addition, vision impairment has reportedly resulted in an economic burden of US$411 billion.[2] As such, the need for solutions to combat vision loss has gained increasing traction.

Patients have preferred topical delivery of ocular drugs as the drug administration method over others, such as intraocular delivery and intravitreal injection. This preference could be attributed to the ease of non-invasive administration and better patient adherence. Nevertheless, the distinctive structure and function of the eye significantly limit the absorption of ocular medications, with bioavailability often being below 5%. The primary obstacles hindering progress in drug delivery are the static ocular barriers located within the posterior and anterior segments of the eye (**Figure 1**).[3] Developing effective strategies to bypass these barriers has been a longstanding challenge for researchers.

In response to these challenges, drug nanodelivery systems have emerged as a novel drug delivery method. Nanodelivery systems offer several advantages, such as prolonged ocular residence times, increased corneal permeability, and sustained drug release, making them an attractive drug delivery modality. This review explores various drug nanodelivery systems, such as microemulsions, solid lipid nanoparticles, nanoemulsions, liposomes, *in situ* gels, dendrimers, exosomes, metal-organic frameworks (MOF), and nanocrystals, designed to overcome the challenges caused by the eye's anatomy and physiology (**Figure 2**).

2. Barriers to ocular delivery

The human eye functions as a sensory organ responsible for detecting and processing visual input. The eye consists primarily of two regions, the posterior and anterior segments. The cornea, conjunctiva, ciliary body, aqueous humor, and lens collectively form the anterior segment of the eye. The posterior segment consists of the retina, sclera, and choroid. Following topical drug administration, the majority of the active ingredients are eliminated by the precorneal tear film.[4] The tear film consists of a lipid layer and an aqueous mucous layer; the amphiphilic properties of the tear film hinder the penetration of purely hydrophilic and hydrophobic substances. Despite being the most widely utilized method for ocular drug delivery, topical administration suffers from low bioavailability (1 – 5%) in the anterior segment due to the combined effects of tear film clearance and eyelid blinking. These physiological factors not only limit drug absorption but may also necessitate frequent dosing to maintain therapeutic levels. Furthermore, nasolacrimal drainage into the systemic circulation after instillation could also result in decreased bioavailability and undesired side effects.[5] The administration process may induce irritation or discomfort, triggering reflex tear flow that further decreases drug retention and negatively impacts patient compliance.

The three principal layers of the cornea include the epithelium, stroma, and endothelium. The cornea is a negatively charged membrane at physiological pH; thus, positively charged molecules can penetrate the cornea more easily than negatively charged molecules. The corneal epithelium is composed of basal cells, wing cells, and squamous cells, all of which are interconnected by tight junctions that restrict the diffusion of larger molecules. The endothelium is notably hydrophobic and is the most significant barrier to drug penetration. Positioned between the aqueous humor and the stroma, the corneal endothelium facilitates the transport of macromolecules between these layers. The endothelium, like the epithelium, is hydrophobic and consists of tightly packed cells, albeit it is formed by a monolayer of flattened epithelial-like cells. The epithelium and endothelium form the blood-aqueous barrier, which serves to limit the selective diffusion of different solutes through the neighboring cells.[6] In contrast to the corneal epithelium and endothelium, the stroma is hydrophilic and is formed by tightly packed collagen. The hydrophilic nature of the stroma allows it to serve as a barrier, preventing hydrophobic molecules from passing deeper into the eye. This biphasic environment indicates that the cornea requires ocular formulations with amphipathic properties and dual-phase solubility for ocular administration.

The conjunctiva is another part of the anterior segment. It is a transparent and thin membrane, which has been noted to be more permeable to drugs than the cornea. Hydrophilic drugs are more permeable to the conjunctiva, though it is uncertain whether hydrophobic drugs are less permeable. The ciliary body, composed of smooth muscle, serves two key roles: The secretion of aqueous humor – which delivers nutrients to avascular tissues and regulates intraocular pressure – and waste drainage from the cornea and lens, including ocular drugs. Drug elimination in the anterior segment is facilitated by the aqueous humor turnover, which is secreted by the ciliary body.

Similar to the anterior segment, drug delivery to the posterior segment of the eye is challenging due to the presence of multiple barriers. The sclera, the white outer layer of the eye, is a long tissue located slightly below the conjunctiva. It is primarily made up of an extracellular matrix consisting of collagen fibrils and glycoproteins.[7] Compared to the cornea, the sclera permits greater solute diffusion, mainly through transscleral diffusion, allowing larger molecules to traverse the porous spaces within the collagen structure, which ranges in diameter from 25 to 300 nm. It is important to note that transscleral permeability is significantly affected by molecular charge, with negatively charged molecules exhibiting higher permeability through the sclera compared to positively charged ones. The choroid, found between the sclera and retina, contains a dense network of capillaries and is reinforced by the Bruch's membrane. It is a vascular tissue that mainly supplies nutrients to the retina. The Bruch's membrane-choroid complex acts as a stronger barrier to drug delivery than the sclera through the transscleral route. It is also more selective than the sclera, as solutions tend to bind to the tissue, thereby reducing overall drug efficiency.[8]

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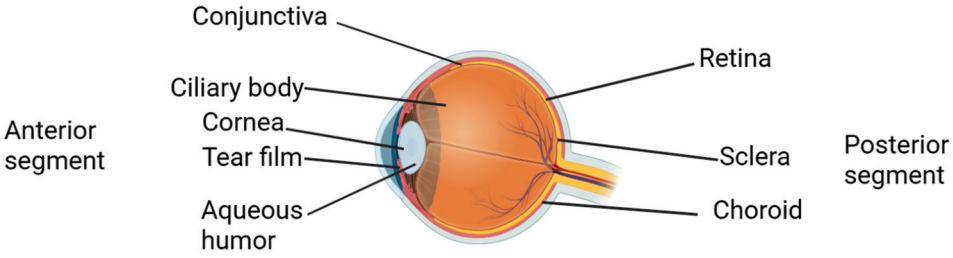

Figure 1. Anatomical barriers to ocular drug delivery. The illustration categorizes key components of the anterior and posterior eye segments that hinder effective drug transport, such as the tear film, cornea, and retina. Understanding these physiological barriers is crucial for designing efficient ocular delivery strategies. Artwork created with BioRender (https://BioRender.com/n50y555).

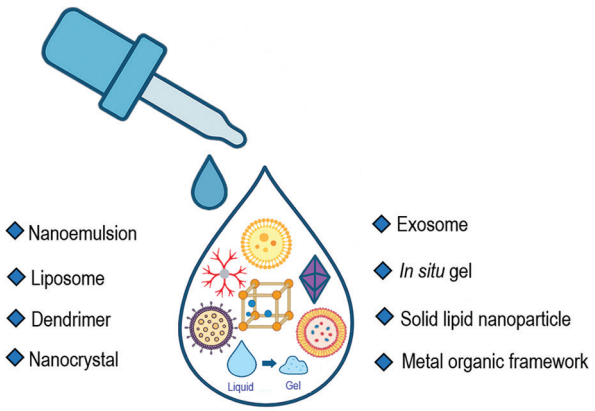

Figure 2. Overview of drug nanodelivery systems explored in this review for ocular drug delivery, each offering specific advantages in enhancing ocular drug bioavailability and retention. Artwork generated with ChatGPT and external design tools.

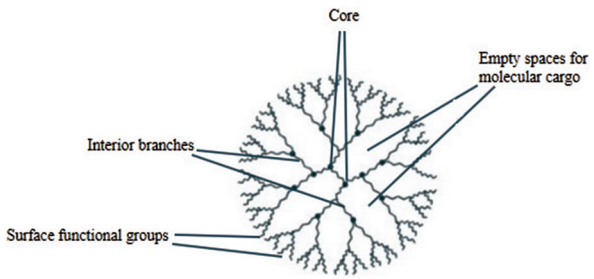

Figure 3. General architecture of a poly(amidoamine) dendrimer, highlighting its branched structure and drug-encapsulating interior. Artwork created with BioRender (https://BioRender.com/n50y555).

Table 1. Ocular barriers of the eye

Segments of the eye	Description
Posterior segment of the eye	
Retina	Hinders the entry of large molecules due to multiple layers
Sclera	Permeability is predicated on the charge of the molecule
Choroid	Part of the Bruch's membrane-choroid complex, which acts as an entry barrier
Anterior segment of the eye	
Cornea	Corneal epithelium hampers large molecules. Corneal endothelium is similar to epithelium and forms the blood-aqueous barrier
Stroma	Hinders the entry of hydrophobic molecules
Conjunctiva	Seemingly more permeable to hydrophilic drugs
Ciliary body	Secretes aqueous humor and drains drugs from the cornea and lens
Aqueous humor	Aqueous humor turnover eliminates drugs
Tear film	Amphiphilic properties of the tear film hinder the penetration of ocular drugs

The retina is a transparent, thin layer of photoreceptor cells situated in the innermost region of the eye. It consists of the inner neural retina and the retinal pigment epithelium. The retina has been observed to progressively hinder the entry of larger molecules due to the multiple layers that form the retinal pigment epithelium and inner neural retina.[9] **Table 1** provides a summary of the major ocular barriers in the anterior and posterior segments that restrict drug penetration and bioavailability.

3. Types of nanodelivery systems used in ocular therapy

3.1. Dendrimers

Dendrimers are a class of star-shaped, nano-sized polymers with a branching web-like structure. They possess a terminal end group on each branch that can be modified for functionalization. They are mainly used to increase the specificity of compounds by altering the pharmacokinetic and pharmacodynamic properties of a drug.[10] For ocular delivery, specifically, it is effective when incorporated into hydrogels and when combined with polyethylene glycol groups, using it primarily for targeted drug delivery.[11] **Figure 3** shows the most used structural basis for dendrimers, which is the poly(amidoamine) structure. The most common synthesis methods for dendrimers are categorized into convergent, divergent, or click chemistry approaches. For the divergent method, several monomeric modules are assembled and added to a core site, allowing it to grow and build outward in a branch-upon-branch structure according to certain dendritic rules and principles. However, there are several drawbacks to this method, such as side or incomplete reactions, resulting in structural defects.[12] To overcome these drawbacks, the convergent method was created, whereby several dendrons are reacted with a multi-functional core to form a dendrimer. Although the convergent method mitigated the issue regarding structural defects, it also possesses several challenges, including limited reactivity between the dendrons and the molecular nucleus due to distance, and decreased reactivity of the central

dendrons.[13] Click chemistry involves the use of copper to join azides and alkyne to synthesize well-defined dendrimers with excellent purity and high yield.[14]

The treatment of diabetic retinopathy often involves invasive procedures, such as intravitreal implants delivering dexamethasone into the eye or intravitreal injections of anti-vascular endothelial growth factor agents. These approaches carry risks of ocular damage, and multiple intravitreal injections may reduce patient compliance. To overcome this issue, Alshammari *et al.*[15] used poly(amidoamine) (PAMAM) dendrimer as a carrier and observed its effects on the ocular bioavailability of the investigational drug ruboxistaurin – a novel drug developed to combat diabetic retinopathy by acting as a protein kinase C beta inhibitor and inhibiting vascular endothelial growth factor release. Invasive drug delivery systems, such as direct injections to the eye, were avoided in this study in favor of non-invasive PAMAM dendrimer nanoparticles, which were designed to improve patient compliance. The PAMAM dendrimer nanoparticles demonstrated favorable drug release profiles and improved stability, and were also theorized to improve patient adherence by reducing the complications associated with invasive delivery methods.

Wang *et al.*[16] formulated novel dendrimer hydrogel particles as a drug delivery carrier for anti-glaucoma drugs, brimonidine tartrate, and timolol maleate. The gel particles in the study presented several advantages, such as low toxicity, the ability to overcome the drug barriers of the eye, and minimal ocular irritation. Compared to plain drug solutions, the nanostructured dendrimer hydrogel particles demonstrated stronger corneal permeation and a greater decrease in intraocular pressure. Among the three dendrimer hydrogel particles that were tested (one nanostructured dendrimer hydrogel particle formulation and two micronized dendrimer hydrogel particles), the nanostructured dendrimer hydrogel particle demonstrated stronger efficacy. Hence, the study suggests its potential use as a carrier for other drugs.

3.2. Liposomes

Liposomes are artificial vesicles that consist of one or more phospholipid bilayers that enclose an aqueous core. Based on its size, it can be categorized into small unilamellar vesicles (10 nm – 100 nm), large unilamellar vesicles (100 nm – 1 μm), and giant unilamellar vesicles (1 μm or above). Unilamellar vesicles have one lipid bilayer surrounding their aqueous core, whereas multilamellar vesicles have one or more lipid bilayers,[17] as displayed in **Figure 4**.

Liposomes have the capacity to encapsulate both hydrophilic and hydrophobic drugs, enabling their cellular uptake through endocytosis. Their dual ability to carry these substances makes them highly suitable for ocular drug delivery systems. Liposomes have demonstrated great efficacy in their ocular delivery to the posterior and anterior segments of the eye. In ocular drug delivery, liposomes offer additional benefits, including extended drug retention and minimal toxicity. However, a notable drawback lies in their low bioadhesiveness, which affects their ocular permeation. This hurdle can be overcome via the integration of bioadhesive polymers such as chitosan.[18,19]

Lai *et al.*[20] addressed the low stability of chrysophanol and berberine hydrochloride, compounds that have been recognized for their potential use in treating age-related macular degeneration.[21,22] A combination of liposomes and polyamidoamine dendrimer (polyamidoamine 3.0) was used as a carrier for both these drugs. The results demonstrated an improvement in the bioavailability of berberine hydrochloride over chrysophanol–berberine hydrochloride suspension. In addition, polyamidoamine-coated liposomes were found to protect against photooxidative stress. However, their effectiveness against age-related macular degeneration requires further investigation using models specifically designed for this condition.

3.3. Nanoemulsions

Nanoemulsions are heterogeneous dispersions of two immiscible liquids and are composed of water, oil, surfactants, and co-surfactants either as oil droplets in water (o/w) nanoemulsion or water droplets in oil (w/o) nanoemulsion (**Figure 5**). Nanoemulsions serve as colloidal drug carriers, with droplet sizes typically ranging between 100 and 500 nm. Nanoemulsions differ from microemulsions in their preparation method. The preparation of nanoemulsions involves the use of thermal and/or mechanical energy, making them less thermodynamically stable. To improve stability, nanoemulsions are often paired with co-surfactants.[23] Nanoemulsions are preferred over their micro counterparts due to enhanced bioavailability, longer drug residence time, and smaller droplet size, leading to better corneal penetration.

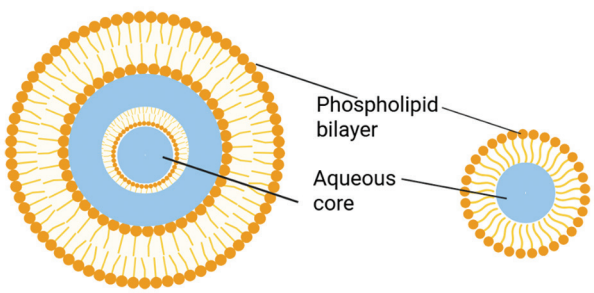

Figure 4. Comparison between unilamellar and multilamellar liposomes showing variations in bilayer configuration. Artwork created with BioRender (https://BioRender.com/n50y555).

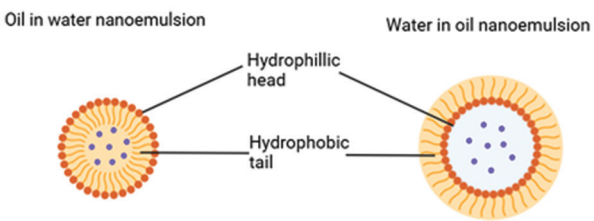

Figure 5. Visualization of oil in water and water in oil nanoemulsion types. The emulsions are stabilized by surfactant molecules that orient at the oil-water interface, with the system type determined by the dispersed phase. Artwork created with BioRender (https://BioRender.com/n50y555).

Nanoemulsions can be prepared using two approaches: High-energy and low-energy methods. The high-energy method involves mixing the oil, water, and surfactant for a sufficient amount of time; the resulting macroemulsion then undergoes homogenization until a suitable droplet size is achieved.[24,25] An example of a low-energy method is the phase inversion temperature method, whereby changes in the temperature cause changes in the spontaneous curvatures of the surfactant. An o/w emulsion undergoes a phase transition as the temperature rises and water is added, resulting in the formation of water droplets dispersed within the oil phase.

Nanoemulsions are commonly used in ocular drug delivery to improve the retention and bioavailability of hydrophobic or poorly retained drugs. Moxifloxacin, a drug noted for its use in the treatment of bacterial conjunctivitis, is limited by its short residence time in the eye.[26] Youssef *et al.*[27] developed a moxifloxacin-loaded nanoemulsion formulation as well as a mucoadhesive variant and compared them to the commercially available solution. The formulations demonstrated improved permeability of moxifloxacin and increased drug residence time. The mucoadhesive variant was suggested to increase patient compliance by reducing the frequency of dosing.

3.4. Cationic nanoemulsions

Cationic nanoemulsions are biphasic formulations characterized by positively charged nanodroplets in a continuous phase. For example, in an o/w nanoemulsion, positively charged oil droplets are dispersed within the aqueous phase.[28] To maximize electrostatic attraction, cationic nanoemulsions are formulated with positively charged nanodroplets that interact with the negatively charged ocular mucosa. These interactions have been found to prolong drug retention in the eye, thereby enhancing therapeutic effectiveness.[29] Concerns regarding cationic nanoemulsions include possible irritation and toxicity due to overuse of the cationic charge inducer.[30,31]

To address the solubility limitations of non-steroidal anti-inflammatory drugs in the treatment of dry eye disease, Jurišić Dukovski *et al.*[32] developed an ibuprofen-loaded cationic nanoemulsion. The cationic o/w nanoemulsion was proven to have sufficient stability, improved drug residence time, and good biocompatibility. Another aim of the study was to stabilize the tear film layer, which is often compromised in dry eye disease.[33,34] This was achieved through the destabilization of the nanoemulsion on encountering the tear film. The oil droplets in the nanoemulsion merged with the tear film lipid layer, while the surfactants integrated into the mucous layer, thereby restoring the tear film's integrity.

Rifampicin is one of the most potent treatments for ocular tuberculosis; however, its clinical utility is hindered by poor solubility in aqueous media.[35] To address this limitation, Bazán Henostroza *et al.*[36] investigated a cationic nanoemulsion loaded with rifampicin. The cationic rifampicin nanoemulsion demonstrated improved drug bioavailability, preserved antimicrobial properties, and enhanced patient quality of life due to reduced frequency of product instillation.

3.5. Solid lipid nanocarriers

Solid lipid nanocarriers are classified into two types: Solid lipid nanoparticles and nanostructured lipid carriers. The key distinction between them is their composition at room temperature. Solid lipid nanocarriers consist of lipids that remain solid, while nanostructured lipid carriers contain a combination of solid and liquid lipids.[37]

Solid lipid nanocarriers are commonly prepared using high-pressure homogenization, solvent emulsification-evaporation, or microemulsion techniques. The high-pressure homogenization method involves using high pressure to push a liquid through a narrow gap, exposing the fluid to shear stress and cavitation forces, causing the particles to break down. The solvent emulsification-evaporation method entails dissolving soluble lipids in a water-immiscible organic solvent, followed by emulsification in an aqueous phase using high-pressure homogenization. Following homogenization, the solvent is evaporated through stirring at room temperature, resulting in the formation of lipid nanoparticles. The microemulsion method involves combining a low-melting-point fatty acid, an emulsifier, and water at a temperature above the melting point of the fatty acid. The mixture is then placed in cold water and continuously stirred.[38]

3.5.1. Solid lipid nanoparticles

Solid lipid nanoparticles are composed of a solid lipid matrix dispersed in an aqueous medium, stabilized by a surfactant layer. Their formulation typically includes biocompatible solid lipids such as fatty acids, fatty alcohols, glycerol esters, and waxes.[39] The layer of surfactants helps stabilize the formulation by reducing interfacial energy between the lipid and aqueous phases during the preparation of solid lipid nanoparticles. Key benefits include low toxicity due to the use of safe excipients, a low production cost, and ease of large-scale production.[40]

Khames *et al.*[41] tested natamycin-loaded solid lipid nanoparticles to address the poor corneal penetration of natamycin, which is used to combat keratitis. The findings indicated that natamycin-loaded solid lipid nanoparticles exhibited enhanced efficacy compared to conventional natamycin administration, demonstrating extended drug release and superior antifungal activity against the primary fungal pathogens responsible for keratitis.[42,43]

3.5.2. Nanostructured lipid carriers

Nanostructured lipid carriers were developed to overcome the instability issues associated with solid lipid nanoparticles. Nanostructured lipid carriers exhibit a higher loading capacity and stability, as they impede the recrystallization of solid lipids, thus preventing drug expulsion during storage.[44] Notably, nanostructured lipid carriers have been predominantly utilized for the delivery of antifungal agents.[45]

Lactoferrin, a protein found in the immune system, is known to possess antifungal effects and stimulate corneal wound healing via the activation of toll-like receptors.[46] Varela-Fernández *et al.*[47] synthesized lactoferrin-loaded nanostructured lipid carriers and determined their efficacy in keratoconus

treatment. The resulting formulation exhibited low toxicity, sustained release of lactoferrin compared to a lactoferrin-buffered solution, and high stability for up to 3 months.

3.6. *In situ* gelling system

In situ gelling systems are liquid formulations that release encapsulated drugs upon undergoing a solution-to-gel transition when applied to a specific site, such as the eye, in ocular drug delivery.[48] The solution-gel phase transition is based on physiological conditions such as changes in temperature, the introduction of ions, or changes in pH.[49,50] It functions similarly to photocages, which also release encapsulated drugs in response to stimuli (a specific wavelength of light).[51]

3.6.1. Thermosensitive in situ gel

Thermosensitive *in situ* gelling systems are typically single-phase, solution-like systems in an aqueous medium that incorporate thermosensitive polymers containing both hydrophobic and hydrophilic segments.[52,53] These systems undergo a phase transition in response to changes in temperature. When exposed to temperatures above the lower critical solution temperature, the balance between the hydrophobic and hydrophilic parts is disrupted, leading to polymer-polymer interactions and resulting in the solution-gel phase transition (**Figure 6**).[54-56]

Mahboobian *et al.*[56] investigated the use of polymers Carbopol 934 and Pluronic F127, combined with hydroxypropyl methylcellulose to create a thermosensitive *in situ* nano gel for flurbiprofen, a notably insoluble non-steroidal anti-inflammatory agent.[57] Carbopol 934 and Pluronic F127 were reported to enhance gel strength and solubility, respectively.[58-60] The flurbiprofen nanosuspension, prepared using hydroxypropyl methylcellulose, was spray-dried to obtain a dry powder formulation designed to enhance solubility. The resulting *in situ* nano gel formulation demonstrated increased drug and corneal residence times for the flurbiprofen nanosuspension and showed good gelation at physiological temperatures.

Wang *et al.*[61] synthesized a combination of thermosensitive *in situ* gel using carbon dots. Carbon dots have recently garnered traction in the medical field due to their good biocompatibility, low toxicity, and solubility in water.[62] Diclofenac sodium, a non-steroidal anti-inflammatory drug characterized by low ocular bioavailability, was incorporated into the system.[63] The drug delivery system showed potential by minimizing tear elimination, prolonging drug release, and enhancing the bioavailability of diclofenac sodium.

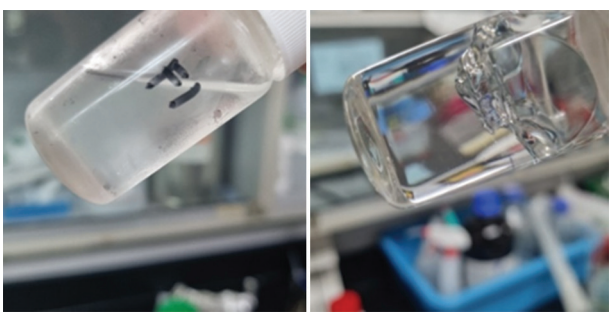

Figure 6. Visual demonstration of a temperature-responsive *in situ* gel system before (left) and after gelation (right). Upon exposure to physiological temperatures, the solution transitions into a gel phase, which prolongs ocular residence and enables sustained drug release.

3.6.2. Ion-sensitive in situ gel

Ion-responsive polymers in ion-sensitive *in situ* gelling systems typically contain ionizable groups.[64,65] These polymers undergo cross-linking with monovalent or divalent cations present in lacrimal fluid, where electrostatic interactions between anionic polymer chains and cations induce a solution-to-gel transformation.[66] The resulting viscosity of the gel is influenced by the concentration of available cations.[67]

Luteolin, a natural flavonoid, has been investigated for its potential benefits in eye health, particularly in managing dry eye disorder.[68] Omran *et al.*[69] developed a carrageenan-based ion-sensitive *in situ* gel by incorporating oleophytocubosomes. Oleophytocubosomes are small, negatively charged particles with high entrapment efficiency[70] for the delivery of luteolin. The ion-sensitive *in situ* gel combined with oleophytocubosomes showed sustained drug release, enhanced anti-glaucoma effects, and improved anti-inflammatory effects.

3.6.3. pH-sensitive in situ gel

The gelation behavior of pH-sensitive *in situ* gel is determined by the measure of acidity, pKa, of the polymer.[71,72] The pH-sensitive polymers are usually either weakly acidic or weakly basic. The solution-gel transition occurs when the pH falls below the pKa value of the weakly acidic polymer and vice versa for the weakly basic polymer.[73,74]

As glaucoma remains a persistent clinical challenge, one of the primary treatment strategies involves reducing intraocular pressure.[75,76] The poor bioavailability of the anti-glaucoma drug, betaxolol hydrochloride,[77,78] in commercial eye drops has prompted the search for more effective ways to administer betaxolol hydrochloride to the eye. Allam *et al.*[79] used niosomes to encapsulate betaxolol hydrochloride combined with a pH-sensitive *in situ* gel. Niosomes are a type of colloidal delivery system similar to liposomes.[80,81] The resulting formulation demonstrated better drug release compared to niosomes or the pH-sensitive *in situ* gel alone. Additionally, the bioavailability and residence time of betaxolol hydrochloride were increased by the formulation when compared to the commercially available eye drops. This innovative delivery system shows promise and may be further explored for its potential in managing glaucoma.

4. Other advancements

Exosomes are double-membrane vesicles secreted by cells that carry molecules such as DNA to target cells. Exosomes can also be engineered and modified to transport drugs to targeted cells. They have been noted to possess several desirable qualities in terms of ocular drug delivery, such as low cytotoxicity, high drug residence time, good targeting capacity, high drug loading capacity, and low immunogenicity.[82] A study conducted by Cao *et al.*[83] utilized a microvascular endothelial cell model to study the therapeutic effects of using exosomes derived

from mesenchymal stem cells for the treatment of diabetic retinopathy. In this study, endothelial-mesenchymal transition and tube formation, processes associated with diabetic retinopathy, were identified through specific molecular markers. It was found that exosomes were able to suppress both endothelial-mesenchymal transition and tube formation by interacting with the microRNA-34a-5p/X-box binding protein 1 signaling pathway, indicating a potential use in the treatment of diabetic retinopathy.

Nanocrystals are nanoparticles that comprise 100% of the crystalline drug after undergoing either the top-down or bottom-up method. A simplified explanation is illustrated in **Figure** 7. The top-down method is based on the reduction in particle size, whereas the bottom-up method is based on building up molecules into small particles. Nanocrystals have been proposed for potential use in ocular applications due to their nanoscale dimensions, which contribute to improved permeability and drug bioavailability.

Nanocrystal-based ocular formulations are a relatively novel concept and have not been fully explored. Kalam *et al.*[84] investigated the potential of nanocrystals for tetragonal zirconia polycrystals, a novel 5-hydroxymethyl-oxazolidinone antibiotic. Tetragonal zirconia polycrystals-nanocrystals were found to have higher solubility in stimulated tear fluid, which indicated superior permeation and bioavailability of tetragonal zirconia polycrystals.

MOFs consist of organic linkers and interconnected metal ions to form a porous structure (**Figure 8**). Nano-sized MOFs possess a high drug loading capacity due to their porous structure. Synthetic modifications of MOFs can enhance their targeting capacity and stability.[85] Gupta *et al.*[86] investigated the potential of MOFs for ocular drug delivery by testing a mucoadhesive MOF loaded with timolol maleate for the treatment of glaucoma. The study's results demonstrated sustained release of timolol maleate, as well as improved drug bioavailability and easy degradation in the eye, resulting in minimal side effects. These results indicate a potential use for MOFs as a drug carrier for other ocular drugs.

5. Role of artificial intelligence (AI)

In recent years, AI and machine learning have emerged as new tools to potentially facilitate the development of ocular drug nanodelivery systems. At a time when the development of novel drug formulations has been observed to be too time-consuming, expensive, and unpredictable, computational pharmaceutics has emerged as a promising approach to reduce this burden by utilizing *in silico* modeling and simulation. The use of AI and machine learning for the development of drug formulations offers several advantages, such as low costs and the elimination of ethical concerns associated with animal testing.

He *et al.*[87] collected data on the size and polydispersity index of drug nanocrystals to construct prediction models using various machine learning algorithms, such as deep neural networks, decision trees, and light gradient boosting machine. The machine learning algorithms were trained on three different preparation methods (ball wet milling, high-pressure homogenization, and antisolvent precipitation). The data used for training was split into three subsets: 80% of the data was used to construct the models, 10% was used for tuning the

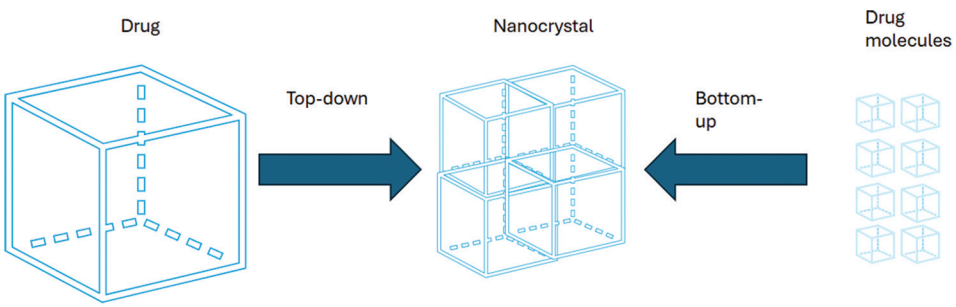

Figure 7. Schematic illustration of two synthetic routes to generate drug nanocrystals: size reduction (top-down) and molecular assembly (bottom-up). Both techniques aim to improve solubility and drug delivery performance in ocular formulations.

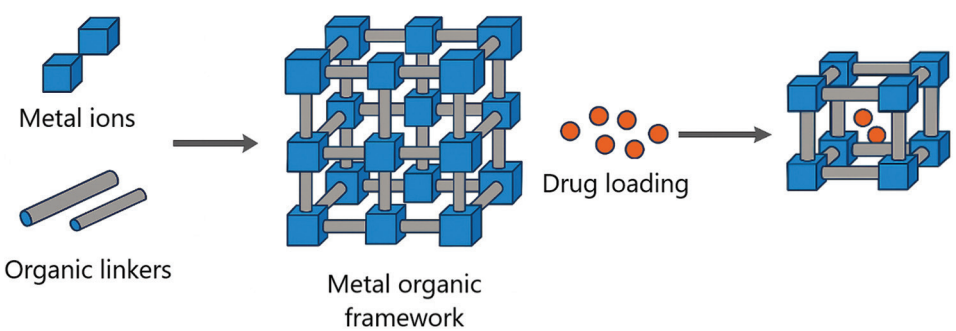

Figure 8. Conceptual workflow of metal-organic framework synthesis and post-synthetic drug loading. Their tunable porosity, high surface area, and modifiability support their use as advanced ocular drug carriers. Artwork created with ChatGPT and design tools.

model hyperparameters to ensure accuracy, and the remaining data was used as a test set for the constructed model against unfamiliar data. The results showed that the light gradient boosting machine displayed the best accuracy among all the other models. The model's efficacy in predicting the outcomes of the high-pressure homogenization method indicates a potential application for accurately forecasting the size and polydispersity index of ocular nanocarriers, including solid lipid nanoparticles, utilizing this method.

German *et al.*[88] utilized a preexisting quasi-three-dimensional model, which had individual eye segments separated into their own domains. The model was able to simulate the topical administration of eyedrops, pharmacokinetics, the physiology of aqueous humor flow, and intraocular pressure levels. The study built upon the quasi-three-dimensional model by constructing the anterior segment of the eye, including the conjunctiva, cornea, aqueous humor, ciliary body, and the lens, and simulating drug loss due to tear film turnover. The model was developed using *in vivo* studies in a rabbit eye model to observe the temporal distribution of timolol in the anterior segment. After validating the model for the rabbit's eye, they altered it to simulate the eye of a human. The predicted distribution over the course of 400 min was similar to the rabbit. The intraocular pressure and its reduction via application of timolol were simulated using an equation from a prior study conducted by a separate team, and the simulated results were compared to the actual results from said study. The intraocular pressure results demonstrated a similar pattern over 400 min to the one conducted by the separate team, with a slight under-prediction, which could be attributed to the remaining timolol concentration in the aqueous humor, preventing the intraocular pressure from returning to baseline. Although the results were satisfactory, the author noted the limitations of the model, as other factors that impact the pharmacokinetics of the eye, such as blinking, were not implemented. Regardless, the model demonstrates potential future use in ocular drug nanodelivery as a more ethical alternative to the use of animal models to study drug residence times.

6. Potential in personalized medicine

Personalized medicine, also known as precision medicine, considers a patient's unique information, such as their genetic profile, lifestyle data, current medical condition, and environmental exposure, to tailor a personalized treatment strategy.[89,90] In ophthalmology, recent studies have utilized printing technologies to construct ocular inserts containing the nanodrug for ocular administration or to use nanoparticles as bioinks for printing onto contact lenses.

Tetyczka *et al.*[91] utilized inkjet printing of itraconazole nanocrystals onto commercially available soft hydrogel contact lenses. Nanocrystals were determined to be ideal, given their good mucoadhesion to the membranes of the eye and the implications of a dual drug release profile in previous studies. Inkjet printing enables personalized dosages by delivering picoliter-scale droplets with high accuracy. The optimal formulation was compared to bulk itraconazole and demonstrated superior performance, attributed to the nanoscale reduction of itraconazole, which enhanced drug solubility and improved inkjet printability. In addition, a dual drug release was observed after 8 h. Notably, visual clarity was preserved by intentionally excluding ink deposition in the central zone of the lens, protecting the pupil.

7. Conclusions

Despite the numerous hurdles that ocular barriers pose for drug administration, the various nanodelivery systems highlighted in this review demonstrate their efficiency and potential for administering drugs to the eye. Although significant strides have been made in nano-based topical drug delivery, future research should focus on improving formulation stability, sustaining drug release, enhancing bioavailability, and ensuring non-toxicity of the mentioned ocular drug delivery systems. Further studies on machine learning are necessary to improve the efficacy of *in silico* modeling, as it has been demonstrated to be a promising step forward for ophthalmology.

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Author contributions
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Ethics approval and consent to participate
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