Characterization and Application of Nanomaterials (2022) Volume 5 Issue 1
doi:10.24294/can.v5i1.1681

REVIEW ARTICLE

Application of nanotechnology in ophthalmology: Where are we?

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ABSTRACT

Nanotechnology is a subject that studies, processes, and applies various functional materials, equipment, and systems, and controls substances on a nanoscale. Nanomedicine refers to its application in diagnosing, treating, preventing, and monitoring various diseases. Drugs administered through eye drops must travel a long distance to avoid various eye barriers reaching the posterior segment of the eye, to achieve the lowest drug level. This review focuses on nanotechnology-based eye disease treatment systems and highlights the obstacles affecting the drug management of eyes and nano-systems for the treatment of eye diseases. This paper summarizes the development prospect of nanotechnology and the challenges it faces in the treatment and diagnosis of ophthalmic diseases, to provide information and new ideas for the implementation of treatment and the development of a refractory eye disease management system.

Keywords: Ophthalmology Nanotechnology; Nanomedicine; Nanoparticles

ARTICLE INFO

Received: 18 January 2022
Accepted: 20 March 2022
Available online: 31 March 2022

1. Introduction

The World Health Organization estimates that in 2018, about 1.3 billion people suffered from some form of visual impairment, mainly due to uncorrected ametropia and cataracts. About 36 million blind people are blind due to cataracts, trachoma, corneal scar, glaucoma, diabetic retinopathy, age-related macular degeneration, and congenital malformations. It is estimated that 80 percent of these cases could have been avoided.

The eyes are divided into anterior and posterior segments. The anterior segment includes the cornea, conjunctiva, anterior chamber, iris, ciliary body, and lens. Eye drops are widely used in the treatment of anterior segment diseases because of their accessibility. However, due to the corneal barrier and the rapid filtration of tears, the bioavailability of topical eye drops is poor. The posterior segment is composed of the choroid, vitreous, and retina. Eye drops must go through a long distance and pass through several eye barriers to reach the posterior pole of the eye, which leads to low bioavailability when the drug reaches its action site[2].

Nanotechnology is a discipline that studies, designs, synthesizes, operates, and applies various functional materials, equipment, and systems, and controls substances at the nanoscale (1–100 nm). According to the National Nanotechnology Initiative, the essence of nanotechnology is the ability to work atom by atom at the molecular level in order to create a huge structure and a new molecular organization. The aim is to develop these properties by controlling structures and devices at the atomic, molecular, and supramolecular levels, and to learn how to

manufacture and use these devices efficiently. It can be used to diagnose, treat, prevent and monitor various diseases.

Nanotechnology is widely used in different fields. For example, in the field of molecular biology, the biological detection method of DNA sequencing is developed through a nanopore sequencer[4,5]. In clinical pharmacology, it is used to prepare nano drugs[6]. Recently, the US Food and Drug Administration approved a number of nano drugs, including polymer nano-particles, polymer-drug conjugates, and degradable polymer structures classified by material type. Their function is to promote the diffusion of drugs through anatomical barriers, improve the bioavailability and half-life of drugs, and promote the controlled release mechanism. It is also used to optimize diagnostic imaging, using inorganic iron oxide nanoparticles as a reagent[7] to enhance image contrast.

The application of nanotechnology in the treatment of eye diseases has become the hope of millions of patients with vision diseases. Nano-carriers and nano suspensions react by releasing drugs at specific sites, thereby reducing the drug dose and minimizing the risk of side effects. For example, brimonidine, cyclosporine, corticosteroids, intravitreal sustained-release implants, etc. In terms of diagnosis and follow-up, noninvasive intraocular pressure measurement for detecting high intraocular pressure and remote monitoring of nanodevices will contribute to the early diagnosis of progressive optic atrophy and clinical monitoring of patients with glaucomatous optic neuropathy[9,10].

In this review, we focus on the eye disease treatment system based on nanotechnology. Firstly, the anatomical structure of the eye and the obstacles to drug administration were briefly introduced. Subsequently, ophthalmic diseases and nano-systems for the treatment of these diseases are reviewed. Finally, the application prospects and challenges of nanotechnology in the treatment and diagnosis of ophthalmic diseases are summarized. This review will provide information and new ideas for the implementation of treatment and the development of a common eye disease management system.

2. Ocular anatomy and ocular barrier

Figure 1 shows nanotechnology delivers ophthalmic drugs through the various ocular anatomical structures. **Table 1** depicts different eye structures and possible therapeutic targets. Its thickness, function, physiology, and composition are emphatically introduced. These special functions can promote or prevent the effect of topical drugs. It also outlines possible action goals to understand the progress of nanotechnology in ophthalmology.

Table 1. Different eye structures and possible therapeutic targets

Obstacle	Barrier thickness	Function	Physiology	Constitution	Other components
Tear film	3 μm thick, 3 μl volume[11]	Lubrication, debris removal, antibacterial protection, stem cell nutrition, and corneal transplantation maintenance; affect the refractive index of the visual system[12].	Dynamic functional units: three chambers (fornication, lacrimal meniscus, and anterior lacrimal membrane). Surfactant and stability of tear film	Lipid component, water component, and mucus component[12].	Immunoglobulin, lysozyme, lactoferrin, OC, and β[14].
Corneal	540–600 μm	A barrier against infection and ocular mechanical injury. Two-thirds of the eye refraction (image perception)[15].	Corneal epithelium: 5–7 layers of non-stratified squamous epithelium are connected by desmosomes and connected through gap junctions, allowing the diffusion of small molecules <1,000 Dalton. It is in direct contact with aqueous humor through the Na^+-K^+-ATPase pump[16] present in endothelial cells.	Avascular lens. Viscoelastic structures are rich in glucosamine and proteoglycans[17]. Sixth floor: Bowman, stroma, Dua layer, Descemet, endothelial layer, corneal epithelium.	Collagen 1, III, V and VIII. Proteoglycans (decorin, lumican, keratin, Mimecan, disaccharide, and fibromodulin) and glycoproteins[15,17].

Table 1. (*Continued*)

Obstacle	Barrier thickness	Function	Physiology	Constitution	Other components
Conjunctival	44.9 ± 3.4 μm	Through mucus, it helps to diffuse the tear film, maintain the stability of the tear film and prevent the adhesion between infection and mucus[19]. Corneal epithelial healing[20].	The outermost layer of the eyeball. Bulbar conjunctiva, eyelid, and forceps. Goblet cells produce mucin[21].	Multilayer non keratinized columnar epithelium (goblet cells) in contact with lamina propria (highly vascularized connective tissue)[21].	TFF1 and TFF3 proteins are involved in the scarring process of corneal tissue[19].
Scleral	0.53 ± 0.14 mm	Viscoelastic properties give eye strength and resistance when intraocular pressure increases[14].	The matrix is composed of proteoglycan, elastin, and large collagen fibers. It is indirectly nourished by the sclera and irrigated by long and short posterior ciliary vessels and choroids. Venous drainage occurs in the vortex vein[22].	Five-sixths of the eye robe. The innermost layer (Lá Mina fusca)[14].	
Use	Iris and ciliary body: 1–2 mm	Iris, light input regulator. Ciliary body: regulates, produces (apigenin) and regulates (electrochemical gradient) aqueous humor flow and secretes hyaluronic acid to the vitreous. Aqueous humor: nutrition of avascular ocular structure, homeostasis of ocular tissue, clearance of metabolites, transport of neurotransmitters, and stability of ocular structure[23].	Ciliary body cornea scleral junction (iris angle): the space where aqueous humor flows from the posterior chamber to the anterior chamber. Aqueous humor contributes to the circulation of inflammatory cells and mediators under pathological conditions and the diffusion of drugs to different tissues[24].	The middle part of the eyeball is composed of the iris, ciliary, body, and choroid. Iris (three layers): posterior iris (pigment epithelium), anterior iris muscle (round or contractile, radial or dilator of the pupil), and matrix (vascularized connective tissue). The ciliary body (flat part and fold part)[24].	Aqueous humor consists of organic and inorganic ions, carbohydrates, glutathione, urea, amino acids, proteins (collagenase, immunoglobulin), oxygen, carbon dioxide, and water[23].
Crystalline	3.5–5 mm	Reflex power (20% of the total eyeball). An image focused on the outside of the retina. Enzyme-mediated oxidant defense mechanisms (glutathione reductase and catalase)[25].	It is nourished by aqueous humor. Metabolic activity is involved in ion exchange through sodium, potassium, calcium, and chloride channels, as well as glucose, amino acids, and antioxidants (glutathione) [26].	No vascular structure, transparent. It is divided into the capsule, crystalline epithelium, cortex, and nucleus. 60% protein (crystalline α, β, γ). It is surrounded by collagen capsules (mainly type IV and XVIII) and laminin, entactin, proteoglycan (heparan sulfate), pearl, and fibronectin. In the banded region, the main components are fibrin and elastin[25,26].	Membrane proteins (different cell connections of lens epithelial cells): Cadherin, calmodulin, type II neural adhesion molecule, endogenous major protein (hydrophobic), and apigenin 0 enzyme (glyceraldehyde 3 phosphate dehydrogenase). The cytoskeleton includes actin, α-actin, anquirina, trompomudulina, myosin, and spectria[25,26].

Table 1. (*Continued*)

Obstacle	Barrier thickness	Obstacle	Barrier thickness	Obstacle	Barrier thickness
Choroid	220–350 µm	Flush the retina and replenish oxygen and nutrition. Absorb light, regulate body temperature, and adjust intraocular pressure by controlling blood flow[27].	Drainage of aqueous humor from the anterior chamber through the uveoscleral pathway (accounting for 35% of its drainage volume)[27].	Blood vessels, melanocytes, fibroblasts, immunocompetent cells, and supporting structures (collagen and elastic connective tissue). Four layers: chorion, chorionic column, two layers of blood vessels, and suprachoroidal[27].	
Vitreous humor	4 cc	Its transparency allows light to pass through the retina and gives the eye structure. Due to its physicochemical properties and ionic charge, it poses obstacles and challenges to drugs working at the posterior pole level[28].		The viscoelastic gel is located between the lens and retina. It contains water (98%), collagen fibers (II, V, IX, and XI), polyureaalic acid, electrolyte (sodium, potassium, calcium, and chlorine), prealbumin, and transfer protein. Equivalent to 80% (4 cc) of eye volume[29.30].	More than 1,205 proteins[30].
Retinal pigment epithelium	0.4–1 mm[31]	The light energy gathered at the macula is absorbed through the ocular refraction system (cornea and lens) to improve the visual quality.	The cell's own DNA repair mechanism includes the defense mechanism against reactive oxygen species[33]. High infusion of chorionic gonadotropin (1400 cc/min/100 g tissue)[34].		Antioxidants: superoxide dismutase and catalase.
Retinal pigment epithelium	0.4–1 mm[31]	Through the melanin in EPR melanosomes, carotenoids (lutein and zeaxanthin), and ascorbic acid in light receptors, photooxidation, and oxidative damage are prevented through the light absorption mechanism[32].	It transports ions and water from subretinal space to chorionic capillaries through the Na^+-K^+-ATPase pump and K^+/Cl^- transporter and maintains intraocular pressure to a certain extent[33,35]		The maintenance of intracellular pH is mediated by the chloride bicarbonate exchanger on the basement lateral membrane of EPR[33].
Retinal nerve sensation		Light transduction of external images[36].	It is perfused by the central retinal artery and receives metabolic input through the choroid[31]. The self-regulation of retinal pressure is mainly mediated by the increase in retinal vascular resistance[37].	The outer membrane (photoreceptor and Muller cell), outer nuclear layer (photoreceptor nucleus), outer plexiform layer (photoreceptor axon), inner nuclear layer (bipolar cell), inner plexiform layer (bipolar cell and amacrine cell), ganglion cell layer, nerve fiber layer, inner limiting membrane (basement membrane formed by Muller cell extension)[31,36].	

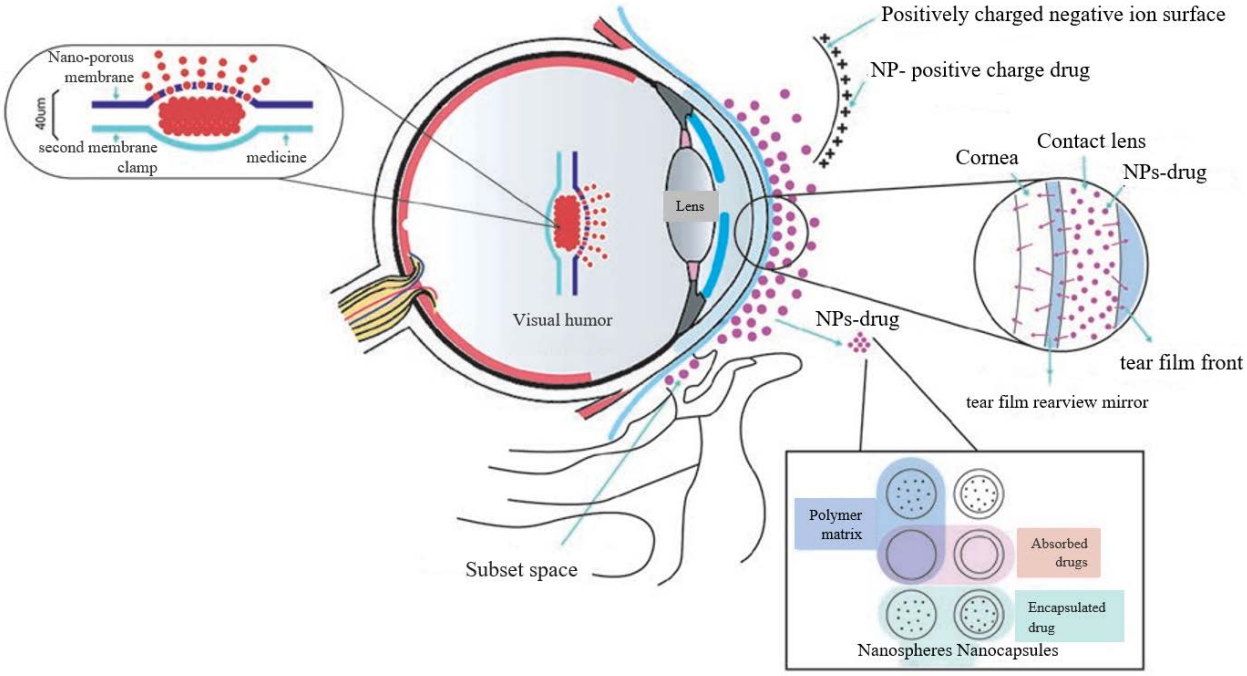

Figure 1. Nanotechnology delivers ophthalmic drugs through different ocular anatomical structures. NP: nanoparticles.

3. Nanotechnology concept

Nanotechnology is a discipline that studies, designs, synthesizes, operates, and applies functional materials, equipment, and systems by controlling nanomaterials (1–100 nm).

The application of nanotechnology in the diagnosis, treatment, and control of various diseases is being implemented rapidly. This new branch of science is called nanomedicine. With the advancement of nanotechnology in medicine and surgery, its application in ophthalmology has made progress. Therefore, new eye nano-systems with different shapes and characteristics to optimize the bioavailability of drugs, prolong the contact time and reduce the eye removal process had been designed[39].

There are many nano-systems that have been applied in the treatment of different eye diseases. Nanoparticle-filled contact lenses with acetazolamide for the treatment of glaucoma[40], biodegradable subconjunctival implants for the treatment of xerophthalmia [41,42], the development of diclofenac eye release nano colloid system based on hydrogel[43,44], polymer nano colloid system for inflammatory diseases[45,46], and nanostructured lipid transporters for controlling drug delivery in ocular infections[47,48].

3.1 Liposome

Liposomes are lipid vesicles comprising one or more phospholipid double chains that surround an aqueous core. According to the size of liposomes and the number of phospholipid double chains, liposomes can be divided into small monolayer vesicles (10 and 100 nm), and large monolayer vesicles (100 and 300 nm) and multi membrane vesicles[49] containing more than one phospholipid double chain. Liposomes are ideal because they encapsulate both hydrophilic and hydrophobic drugs and show good compatibility with eye tissues[50,51]. Examples of applications of such nanoparticles include intravitreal nanoliposome suspensions of prednisolone and infliximab[52,53].

3.2 Polymer nanoparticles

Polymer micelles are self-assembled nanoscopic core-shell structures formed by amphiphilic copolymer inside water. The core/shell structure allows the hydrophobic drug to be encapsulated in its hydrophobic core. Because the core is protected by the hydrophilic crown, the bioavailability of the drug in the local administration of ocular tissue is significantly prolonged[54,55]. An experimental study conducted by Mittal et al. in rabbits showed that timolol maleate was biocompatible with the

cornea, and the intraocular pressure (IOP) decreased for a longer time.[56].

3.3 Nano suspension

Nano suspensions are colloidal dispersions in which the hydrophobic phase is uniformly dispersed in the aqueous medium with the help of surfactant[9]. For example, prednisone, dexamethasone, hydrocortisone, and other corticosteroids have been administered through nanosuspensions to treat anterior inflammation without the expected side effects of high-dose application, such as cataract and glaucomatous optic neuropathy.

3.4 Dendrimer

Dendrimers are monodisperse macro-molecules. Several reaction end groups form an inner cavity around a small molecule. Its tree branch structure presents various repeated terminal groups. In particular, low-generation dendrimers can encapsulate hydrophobic drug molecules in their inner cavities. Due to this unique structure, dendrimers allow the dissolution of drugs with poor water solubility. In addition, dendrimers can be considered real simulations of globular proteins. They are called “artificial proteins” because of their systematicness, electrophoresis, size scale, and other bionic properties[57,58].

Drugs developed using this technology include intravitreal injection of fluocinolone acetoacetate for retinitis pigmentosa and subconjunctival carboplatin for retinoblastoma[59,60].

3.5 Nano micelles

Nano micelles are drug delivery systems composed of hydrophobic nuclei and hydrophilic caps, which allow the dissolution of hydrophobic drugs and produce transparent aqueous preparations when they are ready to be administered to the anterior segment of the eyeball. One of the drugs used in this nanotechnology is cyclosporine. A phase III clinical trial has proved that it is effective, safe, and rapid in the treatment of keratoconjunctivitis sicca[61].

3.6 Niosome

Niosomes are two-layer non-ionic surfactant vesicles that can capture hydrophilic and lipophilic drugs. Niosomes are chemically stable, and their non-ionic properties make them less toxic. Due to its hydrophilic surface, niosomes can easily interact and cross the tear film barrier, so they can reach the cornea/conjunctival tissue[63]. Niosomes have been evaluated as anticholinergic and antibiological agents[62,64,65]. The most important characteristics of the drug delivery carrier for the eye are: (i) the size of the gallbladder is large enough to resist the drainage caused by reflex tear and blinking; (ii) the presence of an irregular shape so that it can be correctly installed at the bottom of the eye bag and accommodated on the surface of the eye; (iii) it is preferable to be heat sensitive and release the drug content in a controlled manner, but at the same time, before removal with blinking and nasolacrimal duct drainage[66,67].

3.7 Cube

The structure of the cube consists of a continuous, highly distorted lipid double chain with two disjoint and consistent waterways. Compared with the simple liposome structure, the cube has increased surface area and the ability to encapsulate various hydrophilic, hydrophobic, and amphiphilic molecules. Due to the strong electric repulsion and the high proportion of liposomes[68–70], cuboids have higher physicochemical stability than liposomes. The use of dexamethasone in eye drops is associated with this nanoparticle, indicating a higher availability of the drug in aqueous humor[71].

3.8 Hydrogel

Hydrogels are a network composed of multifunctional monomers and relays, which react to form a flexible underwater structure. Because the porosity of the hydrogel matrix can be adjusted by changing the crosslinking density, the hydrogel network has been widely studied as a controlled and continuous drug delivery system. The ability to change with the surrounding environment is of great significance for the formation of hydrogels *in situ*. Hydrogels will be crosslinked when the temperature rises from room temperature to body temperature, and their phase-controlled release is affected by pH value or light stimulation[72,73].

Controlled release silicone and hydrogel contact lenses containing timolol are a new technology developed in recent years[74]and have good application prospects.

3.9 Polymer nanofibers

Nanofibers are made of solid fiber materials with a diameter of less than microns. They have a porous structure and a very high surface area.

Nanofibers are nonwoven fiber structures similar to the extracellular matrix. They are composed of highly organized polymer fibers and aqueous compounds comprised of protein polysaccharides to support tissue formation. Therefore, tissue engineering is one of its main applications. The device developed and studied is regenerative therapy. This is to protect the biocompatibility, physiology, and transparency of the cornea[75,76[.

In addition, because the diameter of nanofibers is very small and the surface area is very large, higher drug content can be loaded in a very small part of[77,78] packages.

3.10 Nano preparation for treating eye diseases

Most ophthalmic products on the market are topical preparations for anterior administration. The biggest disadvantage is that only 5% of the injected dose reaches the anterior chamber. Also, the dose penetrating the posterior chamber is small due to multiple and complex anatomical barriers of the eyeball. Nano-sized ophthalmic drugs (**Figure 1**) have the advantages of good solubility, large dissolution area, fast dissolution speed, strong biological adhesion, and strong corneal penetration. It is suggested that the particle size should be less than 10 μm to minimize the irritation to the eye structure and reduce the tear and bleeding of the drip dose, so as to improve the effectiveness of eye treatment.

3.11 Nano suspension

Nano suspension is a submicron colloidal dispersion of pure drug particles in the external liquid phase. An important feature of nanosuspension is to increase the saturated solubility, so as to improve the dissolution rate of compounds. In this system, the drug is bound or dissolved in the structure, encapsulated or captured in the structure by binding to the matrix, and a general drug delivery system is generated, including microemulsion, liposome, niosomes, dendrimer, and cyclodextrin[79,80].

Advantages of using nanoparticles include improved local delivery of macromolecules and low water-soluble molecules, such as glucocorticoids or cyclosporine, for the treatment of immune diseases affecting vision[81]. Other unstable macromolecules, such as nucleic acids, are administered through nanoparticles, providing promising results for gene transfer in the treatment of retinopathy[82,83]. Nanoparticle-mediated drug delivery increases the contact time between the administered drug and the target tissue, such as brimonidine, one of the traditional glaucoma treatment methods, or corticosteroids for the treatment of autoimmune uveitis[78,84]. Some nano-formulations allow the nonsteroidal anti-inflammatory drug indomethacin to reach the posterior internal structure of the eye through a transmucosal pathway[85]. New applications include the use of gold nanoparticles to make the possibility of targeted drug delivery reach specific types of cancer, such as choroidal melanoma, and keep normal cells intact[86].

3.12 Contact lenses

Contact lenses are hard or soft polymer devices designed to directly adapt to the cornea to correct refractive abnormalities. In 1965, Wichterle *et al.*[87] patented the idea of using hydrogel contact lenses as drug delivery devices. The patent refers to the inclusion of drugs in the lens hydration process to provide higher drug availability in use.

Wrapping drug-loaded nanoparticles in the polymer matrix of contact lenses is an effective strategy to prolong drug delivery. The incorporation of drugs is achieved by printing, simple immersion, and colloidal nanoparticles[88–90]. The diameter of nanoparticles must be very small and used in contact lenses to prevent particles from hindering users' vision. Therefore, it is necessary to delay the release of drugs in other ways. This can be achieved by combining the drug with the particles or dispersing the particles through separable chemical bonds so that the affinity of the drug to the particles is greater

than that to the surrounding lens material[89]. This method allows the sustainable release of drugs, which can be adjusted from hours to weeks according to the needs of patients, and allows the treatment of anterior segment lesions.

Different nanoparticles, lead liposomes and microemulsions have been patented, which contain pharmaceutical products and then loaded into contact lenses. Liposomes are used in various drug delivery applications due to their high biocompatibility, transparent permanent lens, and several days of drug release. The initial release is due to the unpackaged drug in the lens. Contact lenses loaded with releasing microemulsion will be administered for 4–8 days, and the initial peak is attributed to the unpackaged drug[89].

In 2013, Jung et al. dispersed timolol nanoparticles in silica gel contact lenses for 30 days. Preliminary studies in beagle dogs have shown promising results in treating glaucoma. The incorporation of nanoparticles into silicon hydrogels leads to the decrease of ion and oxygen permeability and the increase of modulus. The impact on each precursor is directly proportional to the charge of particles[74]. In 2018, Maulvi et al. added gold nanoparticles into contact lenses to improve the absorption of timolol from drug solvent solution, and obtained satisfactory release kinetics *in vivo*, while maintaining the characteristics of contact lenses[91]. The device studied has excellent mechanical properties, and the researchers believe that this material is suitable for administration from daily reusable contact lenses.

3.13 Intraocular implant

Ocular implants are a new treatment method for the controlled release of drugs by reducing the dose and increasing the drug load. In addition, the systemic side effects are lesser and closer to the target site, namely the posterior segment of the eye. Biodegradable or non-biodegradable polymers can be used in eye implant systems. Although biodegradable implants do not need to be removed after implantation into the eye, non-biodegradable implants require additional intervention to remove or fill the implant, which brings additional costs and intraoperative or postoperative surgical risks. The latest development of a biodegradable implant system is the ENV705™ implant Envisia therapeutic agent and Zordera[92] nanoporous membrane device.

The invention discloses a nanoporous membrane skunk device, which comprises two layers of biodegradable waterproof films There are nanopores with the same diameter as the active material on one side, and only one drug molecule is allowed to flow out of the reservoir of each pore at a time. When injecting the device into the vitreous body, it is very thin, only 40 μ m in diameter, and the drug release order is close to 0. When most drugs are released, the polymer layer then degrades, eliminating the need to remove the device. This implant controls the release rate by adjusting the size of the hole and has been shown to last for 4 months. Therefore, it may become the best biodegradable implant for the treatment of chronic retinal diseases[93]. A similar situation occurred when sirolimus was released to the posterior pole[94] through the same device.

3.14 Clinical application

In order to clearly understand the anatomy, histology, and physiology of different eye barriers, as well as the main nanoparticles developed in the research field, **Table 2** lists the most common eye diseases treated with nanotechnology at different action sites of eye tissue and the most influential eye diseases on vision.

4. Expectation

Nanotechnology and nanomedicine are widely used in the field of ophthalmology. In many ways, the use of these devices and nano agents contributes to the bioavailability of drugs, allows diffusion through anatomical barriers which may reduce the side effects of the traditional use of topical ophthalmic drugs, and is likely to reduce invasive intervention to the posterior pole to some extent as well as reducing complications after using some drugs that need surgical treatment. Finally, the benefits of drugs have been optimized and the negative effects have been reduced, opening a huge window within the scope of so-called personalized drugs, which likely require further research on people with

Table 2. Common eye diseases and treatment application

Pathology	Drugs/Devices	Therapeutic target	Associated nanoparticles	Mechanism of NP action
Keratitis	Ofloxacino, colirios, Aciclovir[95]	Fluoroquinolone. Inhibition of topoisomerase II and IV. Herpes polymerase DNA inhibitor	Polyethylene glycol oxide and Eudragit® in the form of microspheres Acyclovir drug encapsulated by polylactic acid microspheres	Improve the bioavailability and controlled release of antibiotics. Delay the degradation of acyclovir prodrug
Conjunctivitis	Tobramicina, colirios[96]	Inhibit the synthesis and binding of polypeptides in ribosomes.	Solid lipid NP	They increase the bioavailability of the corneal surface and help retain it in the conjunctival sac
Dry keratoconjunctivitis	Ciclosporina A, colirios[97]	Immune modulators that prevent T lymphocyte activation.	Chitosan	Sustained release carrier
Uveitis	Nano suspension of prednisone[52] Subconjunctival prednisolone injection[52] Intravitreal injection of infliximab[53]	Prostaglandin and leukopenia monoclonal antibody synthesis inhibitors that inhibit TNF-α activity.	Submicron colloidal carrier of hydrophobic drugs in surfactant stabilized medium	Sustained release and controlled release of drugs, as well as higher bioavailability and lower toxicity
Cataract	Lithium with metabolic activity[98]	Inhibit ROS activity and regulate the level of H_2O_2 and lipid peroxidation in the surrounding environment.	Deposition of platinum nanoparticles by magnetron sputtering	Inorganic catalytic antioxidant
Glaucoma	Nano transporters: pilocarpine, timolol, carbonic anhydrase inhibitor, acetazolamida, dorzolamida, brinazolamida and brimonidina[99] Silicone and hydrogel contact lenses hydrogel contact lenses containing thymolol[74] Thymolol-containing contact lenses[91] Wireless sensors[95]	Traditional treatment of non-selective β-blockers to reduce aqueous humor. Continuous intraocular pressure monitoring.	Dendrimers, liposomes, nanocapsules, nanospheres, hydrogels PGT (triglyceride) NP gold	Drug sustained release increases the loading and absorption of the thymus
Wet DMRE	Hyaluronic acid implant: Bevacizumab[100] Nanopore devices: ranibizumab biodegradable[92]	Humanized monoclonal antibody against vascular endothelial growth factor.	Chitosan NA	Sustained release vehicle Drug release through nanopores
Diabetic retinopathy	Reservoir stimulation response device: nintedanib[101]	Vascular kinase inhibitor, blocking VEGF receptor, platelet-derived growth factor receptor, fibroblast growth factor receptor	Polylactic acid glycolic acid microspheres and nitrobenzene monomer	UV stimulates drug release
Retinitis pigmentosa	Vitreous fluorooctane sulfonate	Microglia activity attenuation.	Polyamide dendritic molecule	Drug sustained release
Retinoblastoma	Subconjunctival carboplatin[60] Photodynamic therapy and vertepofina[102]	Alkylating agent, inhibiting DNA replication, RNA transcription, Dano protein synthesis, selective neovascular endothelial cells, inducing apoptosis and autophagy.	NP dendritic polyamidoamine non-thermal laser activated liposome vertebral body.	Sustained release and controlled release of drugs Reactive oxygen species production and cell death in tumor cells.

Table 2. (*Continued*)

Pathology	Drugs/Devices	Therapeutic target	Associated nanoparticles	Mechanism of NP action
Optic neuromyelitis	Biosensor[104]	NA	Carbon nano-tubes	AQP4 antibody detection.
Endophthalmitis	Damycin, cholinesterase[105]	Anti-gram positive natural lipopeptide antibiotics, including SAMR.	Chitosan	Promote the penetration of antibiotics by opening the connection between corneal cells.

AQP4: antithrombin 4; DMRE: age-related macular degeneration; ERK: extracellular signal-regulated kinase; LIO: intraocular lens; NA: not applicable; NP: nanoparticles; PIO: intraocular pressure; ROS: reactive oxygen species; SAMR: Methicillin-resistant Staphylococcus aureus; VEGFR-2: Vascular endothelial growth factor receptor 2.

individual characteristics, including continuous research on various animal and laboratory models.

Conflict of interest

The authors claim that there is no conflict of interest.

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