Nanotechnology applications in ophthalmology: An update

Aplicaciones de la nanotecnología en el campo de la oftalmología: ¿dónde estamos?

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Abstract

Nanotechnology is a discipline that focuses on the study, processing, and application of several materials, devices, and functional systems, controlling matter at the nanoscale. Nanomedicine refers to its applications for the diagnosis, treatment, prevention and monitoring of different diseases. Topical drug dosage forms for eye conditions must travel a great distance and overcome several eye barriers to reach the posterior segment of the eye, leading to minimum levels of medication. This review focuses on the therapeutic systems for eye diseases based on nanotechnology, emphasizing the barriers that affect the administration of ocular drugs and eye diseases and nanosystems used for their management. The perspective of nanotechnology and the challenges in the treatment and diagnosis of eye diseases are summarized, to provide information and new ideas for implementing treatments and developing management systems for intractable eye diseases.

Key words: Ophthalmology. Nanotechnology. Nanomedicine. Nanoparticles.

Resumen

La nanotecnología es una disciplina que se centra en el estudio, procesamiento y aplicación de diversos materiales, aparatos y sistemas funcionales, y controla la materia a nanoescala. La nanomedicina hace referencia a sus aplicaciones para el diagnóstico, tratamiento, prevención y seguimiento de diferentes enfermedades. Los medicamentos que se administran a través de gotas para los ojos deben viajar una gran distancia y evitar varias barreras oculares para llegar al segmento posterior del ojo, lo que lleva a niveles mínimos de medicamento. Esta revisión se centra en los sistemas terapéuticos para enfermedades oculares basados en nanotecnología, y hace énfasis en las barreras que afectan la administración del fármaco ocular y en las enfermedades oculares y los nanosistemas utilizados para su manejo. Se resume la perspectiva de la nanotecnología y los desafíos existentes en la terapia y el diagnóstico de las enfermedades oculares con miras a proporcionar información y nuevas ideas para implementar tratamientos y desarrollar sistemas de manejo de enfermedades oculares intratables.

Palabras clave: Oftalmología. Nanotecnología. Nanomedicina. Nanopartículas.

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Introduction

The World Health Organization estimated that, in 2018, around 1.3 billion people had some form of visual impairment, and the main causes were uncorrected refractive errors and cataracts. There are approximately 36 million blind people due to cataract, trachoma, corneal scarring, glaucoma, diabetic retinopathy, age-related macular degeneration, and congenital abnormalities. It is estimated that 80% of these cases could have been avoided¹.

The eye is divided into anterior and posterior segments. The anterior segment includes the cornea, conjunctiva, anterior chamber, iris, ciliary body, and lens. The instillation of ophthalmic eye drops is commonly used for the treatment of anterior segment diseases due to its easy accessibility; however, topical eye drops have poor eye bioavailability due to the corneal barrier and rapid tear filtration. The posterior segment is made up of the choroid, vitreous body and retina. Ophthalmic eye drops must travel a long distance and cross several eye barriers to reach the posterior pole of the eye, leading to low bioavailability of the drug when it reaches its site of action².

Nanotechnology is a discipline that focuses on the study, design, synthesis, manipulation, and application of several materials, devices, and functional systems, and controls matter at the nanoscale (1-100 nanometers). According to the National Nanotechnology Initiative, "The essence of nanotechnology is the ability to work at the molecular level, atom by atom, to create a large structure with a fundamentally new molecular organization. The aim is to exploit these properties by gaining control of structures and devices at atomic, molecular, and supramolecular levels and to learn to efficiently manufacture and use these devices"³. It allows applications for the diagnosis, treatment, prevention and monitoring of different diseases.

The applications of nanotechnology are wide, an example is the field of molecular biology to develop bio detection methods of DNA sequencing through nanopore sequencing^{4,5}. In clinical pharmacology, for the creation of nanomedicines⁶; recently, the Food and Drug Administration has approved some nanomedicines, among which are mentioned according to the type of material, polymeric nanoparticles, categorized as conjugates of polymer-drug and architecture of degradable polymers, whose functions are to promote the diffusion of the drug through anatomical barriers, increase the bioavailability and half-life of the drug, as well as favor controlled release mechanisms. It also

has an application in the optimization of diagnostic images, using inorganic iron oxide nanoparticles as a reagent to improve the contrast of images⁷, among others.

The application of nanotechnology-based treatments in ophthalmic diseases is the hope for millions of patients suffering from eye diseases. This is the case of nanotransporters and nanosuspensions. These have the ability to release medications at specific sites, resulting in the use of a lower dose of medication, which minimizes the risk of side effects⁸. Brimonidine, cyclosporine, corticosteroids, sustained-release intravitreal implants, etc. are some examples. At the diagnostic and follow-up level, non-invasive measurement of intraocular pressure (IOP), used to detect high levels of IOP, and remote monitoring by means of nano-scale devices will be of great benefit for the early diagnosis of progressive optic nerve atrophy and clinical surveillance of patients with glaucomatous optic neuropathy^{9,10}.

In this review, we have focused on therapeutic systems for eye diseases based on nanotechnology. First, we summarize a description of the ocular anatomy and the barriers involved in the administration of drugs; later, we review eye diseases and nanosystems used for their management; and finally, we present a brief perspective of nanotechnology and the existing challenges in the therapy and diagnosis of eye diseases. This review will provide information and new ideas for implementing treatments and developing frequent eye disease management systems.

Eye anatomy and ocular barriers

Table 1 presents the different anatomical ocular structures (Fig. 1), and highlights its thickness, functions and physiology, as well as their composition. These special characteristics can facilitate or impede the action of topical ocular medications. Likewise, an overview of possible targets is given, which allows understanding the implementation of nanotechnology advances in ophthalmology.

Nanotechnology concepts

Nanotechnology is a discipline focused on the study, design, synthesis, manipulation, and application of materials, devices, and functional systems, through matter control at the nanoscale level (1-100 nanometers)³⁸.

The use of nanotechnology for the diagnosis, treatment, and control of different diseases has been rapidly implemented. This new scientific branch is called

Table 1. Different eye structures and possible therapeutic targets

Barrier	Barrier thickness	Function	Physiology	Composition	Other components
Tear film	3 μm thick and with a volume of 3 μl ¹¹	Lubrication, debris removal, antimicrobial protection, stem cell nutrition, maintenance of corneal transparency; this influences the refractive power of the visual system ¹² .	Dynamic functional unit: three compartments (fornix, tear meniscus and precorneal tear film). Tear film stabilizing and surfactant properties ¹³ .	Lipid, aqueous and mucin components ¹² .	Immunoglobulins, lysozymes, lactoferrin, α and β ¹⁴ .
Cornea	540-600 μm	Barrier against infections and mechanical injuries to the eyeball. Two thirds of the refractive power of the eye (image perception) ¹⁵ .	Corneal epithelium: 5-7 layers of stratified squamous epithelial cells, held together by desmosomes and communicated by gap junctions that allow the diffusion of small molecules <1,000 Daltons. In direct contact with aqueous humor through aquaporins and $\text{Na}^+ \text{K}^+$ ATPase pumps present in endothelial cells ¹⁶ .	Avascular lens. Viscoelastic structure rich in glycosaminoglycans and proteoglycans ¹⁷ . Six layers: Bowman, stroma, Dua's layer, Descemet, endothelial cell layer, and corneal epithelium ^{15,18} .	Collagen I, III, V and VIII. Proteoglycans (decorin, lumican, keratocan, mimecan, biglycan, and fibromodulin) and glycoproteins ^{15,17} .
Conjunctiva	44.9 $\pm$ 3.4 μm	Through mucin favors the diffusion of tears and maintains the stability of the tear film, prevents infections and adhesion between mucosa ¹⁹ . Corneal epithelium healing ²⁰ .	Outermost layer of the eyeball. Bulbar, palpebral and fornix conjunctiva. Mucin-producing goblet cells ²¹ .	Non-keratinized stratified columnar epithelium (goblet cells) in contact with the lamina propria (highly vascularized connective tissue) ²¹ .	TFF1 and TFF3 proteins are involved in corneal tissue healing process ¹⁹ .
Sclera	0.53 $\pm$ 0.14 mm	Viscoelastic properties that give strength and resistance to the eyeball in case of intraocular pressure elevations ¹⁴ .	Stroma formed by proteoglycans, elastin and large collagen fibers. It is nourished indirectly by the episclera, irrigated by the long and short posterior ciliary vessels, and the choroid. Venous drainage occurs through the vortex veins ²² .	Five sixths of the outer layer of the eye. Inner layer (lamina fusca) ¹⁴	
Uvea	Iris and ciliary body: 1-2 mm	Iris, regulator of the entrance of light. Ciliary body: control of accommodation, production (aquaporins) and regulation (electrochemical gradients) of aqueous humor flow and hyaluronic acid secretion towards the vitreous. Aqueous humor: nutrition of avascular ocular structures, homeostasis of ocular tissues, elimination of products of metabolism, transport of neurotransmitters and stabilization of the ocular structure ²³ .	Ciliary-corneal-scleral body junction (iridocorneal angle): space through which aqueous humor flows from the posterior chamber to the anterior chamber. Aqueous humor facilitates the circulation of cells and inflammatory mediators under pathological conditions, as well as the diffusion of drugs to different tissues. ²⁴ .	Intermediate part of the eyeball made up of: iris, ciliary body and choroid. Iris (three layers): posterior (pigment epithelium), anterior iris muscle (circular or constrictor and radial or dilator of the pupil) and stroma (vascularized connective tissue). Ciliary body (pars plana and pars plicata) ²⁴ .	Aqueous humor composed of organic and inorganic ions, carbohydrates, glutathione, urea, amino acids, proteins (collagenases, immunoglobulins), oxygen, carbon dioxide and water ²³ .

(Continues)

Table 1. Different eye structures and possible therapeutic targets (*Continued*)

Barrier	Barrier thickness	Function	Physiology	Composition	Other components
Lens	3.5-5 mm	Dioptric power (20% of total power). Focus images from the outside on the retina. Enzyme-mediated defense mechanism against oxidizing agents (glutathione reductase and catalase) ²⁵ .	It is nourished from the aqueous humor. Metabolically active, it participates in ion exchange through Na ⁺ , K ⁺ , Ca ⁺⁺ and Cl ⁻ channels, also glucose, amino acids and antioxidants (glutathione) ²⁶ .	Clear, avascular structure. Divided into capsule, lens epithelium, cortex and nucleus. 60% proteins (crystalline α , β , γ). Surrounded by a collagen capsule (mainly type IV and XVIII), as well as laminin, entactin, proteoglycans (heparan sulfate), perlecan and fibronectin. In the zonular region, the predominant composition is due to the presence of fibrillin and elastin ^{25,26} .	Membrane proteins (different cell junctions of lens epithelial cells): N-cadherins, calpactins, type II neuronal adhesion molecules, intrinsic major protein (hydrophobic), and aquaporin 0, enzymes (glyceraldehyde 3 phosphate dehydrogenase). The cytoskeleton contains actin, α -actinin, ankyrin, thrombomodulin, myosin, spectrin ^{25,26} .
Choroid	220-350 μ m	Irrigate the retina, supplying it with oxygen and nutrients. Light absorption, thermoregulation and modulation of intraocular pressure, by controlling blood flow ²⁷ .	Aqueous humor drainage from the anterior chamber, through the uveoscleral route (35% of its drainage) ²⁷ .	Blood vessels, melanocytes, fibroblasts, immunocompetent cells and supporting structure (collagen and elastic connective tissue). Four layers: Bruch's membrane, choriocapillaris, two vascular layers, and the suprachoroid ²⁷ .	
Vitreous humor	4 cc	Its transparency allows the passage of light to the retina and gives structure to the eyeball. It constitutes a barrier and challenge for drugs that act at the posterior pole level given their physicochemical properties, as well as their ionic charge ²⁸ .		Viscoelastic gel located between the lens and the retina, water (98%), collagen fibers (II, V, IX and XI), poly hyaluronic acid, electrolytes (sodium, potassium, calcium, chlorine), prealbumin, transferrin. Corresponds to 80% (4 cc) of eye volume ^{29,30} .	More than 1,205 proteins ³⁰ .
Retinal pigment epithelium (RPE)	0.4-1 mm ³¹	Improves visual quality by absorbing concentrated light energy in the macula through the eyeball refraction systems (cornea and lens). Avoids photo-oxidation and oxidative damage through light absorption by means of the melanin contained in the RPE melanosomes, carotenoids (lutein and zeaxanthin), and ascorbate contained in photoreceptors ³² .	Cellular DNA repair mechanisms involved as defense mechanisms against reactive oxygen species ³³ . High blood perfusion of the choriocapillaris (1,400 cc/min/100 gr of tissue) ³⁴ . Transports ions and water from the subretinal space to the choriocapillaris through Na ⁺ K ⁺ ATPase pumps and K ⁺ /Cl ⁻ transporters, maintaining to some extent intraocular pressure ^{33,35} .		Antioxidant agents: superoxide dismutase and catalase. The maintenance of intracellular pH is mediated by the chloride-bicarbonate exchangers located in the RPE basolateral membrane ³³ .

(Continues)

Table 1. Different eye structures and possible therapeutic targets (*Continued*)

Barrier	Barrier thickness	Function	Physiology	Composition	Other components
Sensorineural retina		Phototransduction of external images ³⁶ .	Irrigated by the central retinal artery and receives metabolic nutrients through the choroid ³¹ . Self-regulation of retinal pressure is primarily mediated by increased vascular resistance of the retinal vessels ³⁷ .	Outer limiting membrane (photoreceptor and Müller cell bodies), outer nuclear layer (photoreceptor nuclei), outer plexiform layer (photoreceptor axons), inner nuclear layer (bipolar cells), inner plexiform layer (bipolar and amacrine cells), ganglion cell layer, nerve fiber layer, internal limiting membrane (basement membrane formed by Müller cells extensions) ^{31,36} .	

Table 2. Frequent eye disorders and therapeutic applications

Disorder	Medication/device	Therapeutic target	Associated nanoparticle	NP mechanism of action
Keratitis	Ofloxacin, eye drops ⁹⁵ Acyclovir ⁹⁵	Fluoroquinolone. Inhibition of topoisomerase II and IV. Herpes virus DNA polymerase inhibitor	Polyethylene oxide and Eudragit® in the form of microspheres Acyclovir prodrugs encapsulated in polylactic-co-glycolic acid microspheres	Increased bioavailability and controlled release of the antibiotic Delays breakdown of acyclovir prodrugs
Conjunctivitis	Tobramycin, eye drops ⁹⁶	Inhibition of the synthesis and binding of polypeptides in the ribosome	Solid lipids NP	Increase the bioavailability on the corneal surface and favor its retention in the conjunctival sac
Keratoconjunctivitis sicca	Cyclosporin A, eye drops ⁹⁷	Immunomodulator that prevents T-lymphocyte activation	Chitosan	Sustained release vehicle
Uveitis	Prednisolone nanosuspensions ⁵² Subconjunctival prednisolone injection ⁵² Intravitreal infliximab ⁵³	Inhibitor of the synthesis of prostaglandins and leukotrienes Monoclonal antibody that inhibits TNF- α activity	Submicron colloidal vehicle for hydrophobic drugs in a medium stabilized by surfactants Pegylated liposomal formulation Liposomal transporter	Prolonged and controlled release of the drug, as well as greater bioavailability and less toxicity
Cataract	IOL with metabolic activity ⁹⁸	Inhibit the activity of ROS and regulate the levels of H ₂ O ₂ and lipid hydroperoxides in the surrounding medium	Platinum nanocoating deposited by a magnetron sprayer	Catalytic inorganic antioxidant

(Continues)

Table 2. Frequent eye disorders and therapeutic applications (*Continued*)

Disorder	Medication/device	Therapeutic target	Associated nanoparticle	NP mechanism of action
Glaucoma	Nano transporters of: pilocarpine, timolol, carbonic anhydrase inhibitors, acetazolamide, dorzolamide, brinzolamide, brimonidine ⁹⁹ Timolol-containing silicone and hydrogel contact lenses ⁷⁴ Timolol contact lenses ⁹¹ Wireless sensors ⁹⁵	Drugs used in traditional glaucoma treatment Non-selective β -blocker that decreases the production of aqueous humor Continuous IOP monitoring	Dendrimers, liposomes, nano capsules, nanospheres, hydrogels PGT (Propoxylated glyceryl triacrylate) Gold NP	Prolonged drug release Prolonged drug release Increase timolol load and absorption
Wet AMD	Hyaluronic acid: bevacizumab implant ¹⁰⁰ Biodegradable Nano porous Film Device: ranibizumab ⁹²	Humanized monoclonal antibody against vascular endothelial growth factor	Chitosan NA	Sustained release vehicle Release of the drug through nanopores
Diabetic retinopathy	Stimulus-responsive reservoir device: nintedanib ¹⁰¹	Angiokine inhibitor, blocking VEGF receptors, platelet-derived growth factor receptors, and fibroblast growth factor receptors	Poly(lactic-co-glycolic acid) microspheres and nitrobenzyl monomers	Drug release through ultraviolet light stimulation
Retinitis pigmentosa	Intravitreal fluocinolone acetonide ⁵⁹	Attenuation of microglial activity	Polyamidoamine dendrimers	Sustained drug release
Retinoblastoma	Subconjunctival carboplatin ⁶⁰ Verteporfin photodynamic therapy ¹⁰²	Alkylating agent, inhibits DNA replication, RNA transcription, and protein synthesis Selective damage to neovessel endothelial cells, apoptosis and autophagy inducer	Dendrimeric polyamidoamine NP Activation of liposomal verteporfin by a non-thermal laser	Prolonged and controlled drug release ROS production and cell death on tumor cells
Retinopathy of prematurity	Intravitreal gold NP ¹⁰³	NA	Gold NP	Suppression of the VEGFR-2 signaling pathway by autophosphorylation and blocking activation of ERK1 and 2
Optic neuromyelitis	Biosensor ¹⁰⁴	NA	Carbon nanotubes	AQP4 antibody detection
Endophthalmitis	Daptomycin, eye drops ¹⁰⁵	Natural lipopeptide antibiotic against gram-positives, including MRSA	Chitosan	Promotes penetration of the antibiotic by opening the intercellular junctions of the cornea

AMD: age-related macular degeneration; ERK: kinase regulated by extracellular signals; IOL: intraocular lens; NA: not applicable; NP: nanoparticles; IOP: intraocular pressure, ROS: reactive oxygen species; MRSA: Methicillin-resistant *Staphylococcus aureus*; VEGFR-2: vascular endothelial growth factor receptor 2.

Figure 1. Administration of ophthalmic drugs by nanotechnology through the different ocular anatomical structures. NP: nanoparticles.

nanomedicine. The evolution of knowledge about nanotechnology in medical-surgical areas has allowed the progress of applications in ophthalmology. Thus, novel ocular nanosystems have been designed in different ways and with specific characteristics to optimize drug bioavailability, by improving contact time and decreasing the clearance process³⁹.

There are many nanosystems. Among others, nanoparticle-loaded contact lenses to administer acetazolamide in the treatment of glaucoma⁴⁰, biodegradable subconjunctival implants to administer cyclosporin A for the treatment of dry eye syndrome^{41,42}, development of hydrogel-based nano colloidal systems for the ocular release of diclofenac^{43,44}, polymeric nano micellar systems for inflammatory diseases^{45,46}, and nanostructured lipid transporters for the controlled supply of ocular drugs for infections^{47,48}.

Liposomes

Liposomes are lipid vesicles, with one or more phospholipid bilayers, that enclose an aqueous nucleus. Depending on their size and the number of phospholipid bilayers, liposomes can be classified into small unilamellar vesicles (10 and 100 nm), large unilamellar vesicles (100 and 300 nm), and multilamellar vesicles,

which contain more than a single phospholipid bilayer⁴⁹. Liposomes are ideal because they encapsulate both hydrophilic and hydrophobic drugs and demonstrate very good compatibility with ocular tissues^{50,51}. Examples of such nanoparticles are prednisolone nanosuspensions and intravitreal infliximab with liposomal nanocarrier^{52,53}.

Polymeric nanoparticles

Polymeric micelles are core/shell structured nanoparticles formed by the self-assembly of amphiphilic copolymers. The core/shell structure allows the encapsulation of hydrophobic drugs in their hydrophobic core. Because the nucleus is protected by the hydrophilic crown, drug bioavailability is significantly prolonged when it is administered topically to ocular tissues^{54,55}. An experimental study developed by Mittal, et al. with topical timolol maleate in rabbits, showed biocompatibility with the cornea and decreased IOP for longer times⁵⁶.

Nanosuspensions

They are colloidal dispersions in which hydrophobic drugs are uniformly dispersed in an aqueous medium with the help of surfactants⁹. Prednisone, dexamethasone,

hydrocortisone, and other corticosteroids, for example, have been administered through nanosuspensions for the treatment of anterior segment inflammation, without the expected side effects of high-dose applications, such as in cataract and glaucomatous optic neuropathy.

Dendrimers

Dendrimers are monodispersed macromolecules with several reactive end groups that surround a small molecule and form an internal cavity. Its branched tree-like architecture features a variety of repetitive end groups. Especially low-generation dendrimers can encapsulate hydrophobic drug molecules in their internal cavities. Due to this unique structure, dendrimers allow the solubilization of drugs that are poorly soluble in water. Furthermore, dendrimers can be considered as a true imitation of globular proteins. They are known as «artificial proteins», based on their systematic, electrophoretic, dimensional scale properties, and other biomimetic properties^{57,58}.

Drugs developed with this technology include intravitreal fluocinolone acetonide for the treatment of retinitis pigmentosa, and subconjunctival carboplatin for retinoblastoma management^{59,60}.

Nano micelles

They are drug delivery systems composed of a hydrophobic core and a hydrophilic shell, which allow the dissolution of hydrophobic drugs, with the generation of a clear aqueous formulation for drug administration in the anterior segment of the eye. One of the drugs administered with this type of nanotechnology is cyclosporine. A phase III clinical trial demonstrated its effectiveness, safety, and rapid action in the treatment of keratoconjunctivitis sicca⁶¹.

Niosomes

Niosomes are double-layered nonionic surfactant vesicles, which can trap hydrophilic and lipophilic drugs. Niosomes are chemically stable and their nonionic nature facilitates their low toxic potential⁶². Thanks to their hydrophilic surface, niosomes easily interact and cross the tear film barrier, and as a result they can reach corneal/conjunctival tissue⁶³. Niosomes have been evaluated as anticholinergics, anti-glaucomatous, and antibiotics^{62,64,65}. The most determining characteristics for use as vehicles for the administration of ocular drugs are: the size of the vesicle, large enough to resist drainage by reflex tearing and blinking; irregular shapes

that allow correct placement into the cul-de-sac and permanence on the ocular surface; be heat-sensitive to release the content of the drug in a controlled manner, but at the same time, before being removed through blinking and nasolacrimal drainage^{66,67}.

Cubosomes

The structure of the cubosome consists of a highly twisted continuous lipid bilayer, with two congruent non-crossing water channels. Compared to the simple bilayer structure of liposomes, cubosomes have an increased surface area and a great ability to encapsulate various molecules of hydrophilic, hydrophobic, and amphiphilic substances. Cubosomes have a higher physical-chemical stability than liposomes, due to the strong electrical repulsion and a large proportion of lipid bilayer⁶⁸⁻⁷⁰. The use of dexamethasone eye drops, associated with this type of nanoparticle, evidences a greater availability of the drug in the aqueous humor⁷¹.

Hydrogels

They are a network of multifunctional monomers and relays that react to form a flexible structure loaded with water. Hydrogel networks have been extensively studied as a controlled and sustained drug delivery systems, since the porosity of their matrix can be adapted by changing the density of the crosslinking. This ability to change depending on the surrounding environment has important implications for *in situ* formed hydrogels, those that cross-link when the temperature increases from room temperature to body temperature, as well as the controlled release of drugs as a result of pH or photostimulation^{72,73}. Controlled-release timolol-containing silicone and hydrogel contact lenses are a promising newly developed technology⁷⁴.

Polymeric nanofibers

Nanofibers are solid fibers of materials that have diameters below the micron range, with a porous structure and a very high surface area.

Nanofibers are nonwoven fibrous structures, similar to the extracellular matrix, consisting of an aqueous compound of highly organized polymeric fibrils and proteoglycans to support tissue formation. For this reason, one of its main applications is in tissue engineering. Keratoprosthesis are devices for which studies have been conducted with the aim to safeguard the

biocompatibility, physiology and, therefore, the most important property of the cornea, its transparency^{75,76}.

Additionally, due to their very small diameter and exceptionally high surface area, nanofibers allow loading a significantly higher drug content into a very small portion of a patch^{77,78}.

Nano formulations for the treatment of eye diseases

Much of the ophthalmic products on the market are topical formulations for the administration of drugs to the anterior segment. The biggest disadvantage is that only 5% of the instilled dose reaches the anterior chamber, and the one that penetrates the posterior segment is smaller, due to the multiple and complex anatomical barriers of the eyeball. The administration of nano-sized ophthalmic drugs (Fig. 1) represents advantages due to greater solubility, greater dissolution surface available, greater dissolution speed, greater bio adhesion and corneal penetration. The recommendation is that particles measure less than 10 μm to minimize irritation of the ocular structures, decrease tearing and drainage of the instilled dose, and therefore increase the efficacy of ocular treatments.

Nanosuspensions

Nanosuspensions are submicron colloidal dispersions of pure drug particles in an external liquid phase. An important feature of nanosuspensions is the increased saturation solubility and, consequently, an increased dissolution rate of the compound. In this system, drugs are loaded by matrix binding or dissolved, encapsulated or trapped within the framework, generating a versatile drug delivery system that includes microemulsions, liposomes, niosomes, dendrimers and cyclodextrins^{79,80}.

The advantages of nanoparticle use include the improved topical passage of large and poorly water-soluble molecules, such as glucocorticoids or cyclosporine, to treat immunological diseases that affect vision⁸¹. Other large and unstable molecules, such as nucleic acids, administered by nanoparticles, offer promising results for gene transfer therapy in the treatment of retinopathies^{82,83}. Nanoparticle-mediated drug administration increases the contact time of the administered medication with its target tissue, as is the case of bromonidine, one of the traditional treatments for glaucoma, or corticosteroids used to treat autoimmune uveitis^{78,84}. Some nanoformulations have allowed the

non-steroidal anti-inflammatory drug, indomethacin, to reach the posterior internal structures of the eye using the transmucosal route⁸⁵. New applications include the use of gold nanoparticles that allow targeted delivery to reach specific types of cancer, such as choroidal melanoma, without affecting healthy cells⁸⁶.

Contact lenses

Contact lenses are rigid or soft polymeric devices designed to fit directly on the cornea to correct refractive abnormalities. In 1965, Wichterle, et al. patented the idea of using hydrogel contact lenses as drug delivery devices. The patent mentions the inclusion of drugs in lens hydration to offer greater availability of the drug during use⁸⁷.

The inclusion of drug-loaded nanoparticles within the contact lens polymer matrix is an effective strategy for prolonged drug delivery. Drug incorporation is accomplished with methods such as printing, simple soaking, and colloidal nanoparticles⁸⁸⁻⁹⁰. Nanoparticle diameter must be extremely small for use in contact lenses to prevent particles from obstructing the user's vision. Therefore, it is necessary to delay the release of the drug through other means. This can be accomplished by linking the drug to the particle through a cleavable chemical bond or by designing a particle that allows a higher affinity of the drug for the particle than for the material of the surrounding lens⁸⁹. This approach allows sustained release, which can be adjusted to the patient's needs, from a few hours to several weeks, enabling the treatment of pathologies of the anterior segment.

Different nanoparticles have been patented, especially liposomes and microemulsions that contain the drug and are then loaded into contact lenses. Liposomes have been used in several drug delivery applications due to their high biocompatibility; lenses remain clear and release the drug for a few days, with an initial release that is attributed to the non-encapsulated drug present in the lens. Contact lenses loaded with microemulsions will release the drug for 4 to 8 days, with an initial peak attributed to the non-encapsulated drug⁸⁹.

In 2013, Jung, et al. dispersed the timolol nanoparticles of PGT (propoxylated glyceryl triacrylate) in silicone contact lenses to administer the drug for 30 days. Preliminary studies in Beagle dogs showed promising results for glaucoma. The incorporation of nanoparticles in silicone hydrogels caused a reduction in ion and oxygen permeability and an increase in modulus; the impact on each of these properties was proportional to particle charge⁷⁴. In 2018, Maulvi, et al. incorporated

gold nanoparticles into contact lenses and improved the absorption of timolol from the drug's solvent solution along with satisfactory dynamic and kinetic results *in vivo*, without altering the properties of the lens⁹¹. The evaluated devices exhibited excellent mechanical properties, and the researchers propose that the material is suitable for the supply of drugs from reusable daily contact lenses.

Intraocular implants

Eye implants are new treatments that seek the controlled release of drugs, through higher dosages and drug loads. In addition, there are systemic side effects and greater proximity to the target site, the posterior segment of the eye. Biodegradable or non-biodegradable polymers can be used in implantable eye systems. Biodegradable implants do not need to be removed after insertion into the eye, but non-biodegradable implants require an additional intervention for removal or filling, carrying additional costs, and intra or postoperative surgical risks. The most recent developments in biodegradable implantable systems are the Envisia Therapeutics ENV705™ Implant and the Zordera⁹² nanoporous film device.

The Zordera nanoporous film device consists of a drug in the pellet sealed between two thin waterproof biodegradable membrane layers. One side has nanopores of the same diameter as the active drug substance, allowing only one drug molecule to leave the reservoir of each pore at a time. The device is injected into the vitreous; it is very thin, with a diameter of only 40 µm and a sustained drug release of almost zero-order. The polymer layers degrade at a later time when most of the drug has been released, eliminating the need to remove the device. This implant offers control over the release rate by adjusting pore size, and has demonstrated to administer ranibizumab for four months on a continuous basis. Therefore, it can become the best biodegradable implant to treat chronic retinal conditions⁹³. A similar case occurs with sirolimus release in the posterior segment using this same device⁹⁴.

Clinical applications

After understanding the anatomy, histology and, physiology of the different eye barriers, as well as the main nanoparticles that have been developed in the field of research, Table 2 lists the most frequent eye disorders and those with the greatest negative impact on visual

acuity for which nanotechnology has been used as a treatment targeted for different ocular tissues (Fig. 1).

Perspectives

The range of applications of nanotechnology and nanomedicine in the field of ophthalmology is wide. The use of these devices and nanoformulations favors drug bioavailability, allows diffusion across anatomical barriers, and could decrease the adverse effects attributed to the use of conventional topical eye drugs, and very possibly decrease, to some extent, invasive interventions in the posterior pole, as well as complications secondary to the use of certain medications that require surgical procedures for their implantation. Ultimately, the benefits of drugs are optimized and their negative impacts are reduced, and a large window opens within the spectrum of so-called personalized medicine, which will most likely require new studies with particular designs for populations with individual characteristics, as well as the continuous study in different animal and laboratory models.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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