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Nanotechnology-Ocular Devices for Glaucoma Treatment: A Literature Review

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ABSTRACT

Nanotechnology enabled the development of materials and devices with great utility in different fields of medicine. By using engineered-based nano-devices and structures, human biological systems may be controlled and repaired at a molecular scale, ultimately leading to a biological benefit. In particular, in the field of glaucoma treatment, nanotechnology may, for example, enhance drug residence time on the ocular surface and ocular bioavailability, as well as improve surgical success by both optimizing postoperative scarring and providing a wider safety window. Further studies are still needed to entirely explain the pharmacodynamics of nanotechnology-based therapeutic approaches and prove their biological consequences in human eyes. This review aims to summarize the literature concerning the advances in nanotechnology, specifically regarding ocular devices applied to the treatment of glaucoma.

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Introduction

Glaucoma is a chronic, progressive optic neuropathy, representing the leading cause of irreversible blindness worldwide. By the year 2020, it is estimated to affect near 80 million people, with 11 million people bilaterally blind.^{1–4}

Despite being a multifactorial disease, where a complex combination of risk factors, such as intraocular pressure (IOP), increasing age, genetic, ethnic and structural ocular variations lead to a progressive retinal ganglion cells and axons loss, most of the therapies used nowadays are focused on decreasing IOP, as the only modifiable parameter in the previous equation, in order to decrease disease progression.⁵

Topical IOP-lowering therapies aim to reduce IOP by increasing aqueous humor (AH) drainage or decreasing AH production. However, the requirement of rigid patient compliance, poor intraocular bioavailability and possible association with significant topical and systemic side-effects may turn their administration uninviting.^{5–11}

On the other hand, outflow-increasing surgeries, such as trabeculectomy, glaucoma drainage devices (GDD) implantation, nonpenetrating surgeries and other minimally invasive surgical surgeries, lower IOP by enhancing AH drainage. While more recent techniques are associated with a better predictability in IOP-lowering action and a lower incidence of immediate postoperative complications, abnormal wound healing and scarring still compromise surgical outcomes.^{6,12,13}

In this sense, the emergence of nanotechnology possibly represents an important advance in the therapeutic approach

of glaucoma. By the use of novel nano-devices and particles, AH production and drainage may be modulated at a molecular scale. Nanomaterials exhibit several attractive properties, the most important may derive from its namesake. Indeed, most particles are in the range 1–100 nm. This enables penetration through smaller capillaries and absorption by surrounding cells, allowing an efficient drug accumulation at target sites. Additionally, through a structural high surface area-to-volume ratio arrangement, these particles can be manipulated to present more sites for chemical reactions, have a better biocompatibility and biodegradability profile, a better electrical conductivity and magnetic properties, potentially inducing a more effective response than their larger, unmanipulated counterparts found in nature. Drugs may be attached, dissolved, encapsulated or entrapped on the nanoparticle matrix, overcoming physiological barriers and directing the drug to specific cells or compartments. For these reasons, the interest in the research of nanotechnology applied to the treatment of different diseases, including glaucoma, is growing.^{14–24}

Currently, there are no FDA-approved or clinically available sustained drug delivery systems (DDS) for glaucoma treatment,²⁵ including nanotechnology-based DDS. Also, the majority of ocular devices for glaucoma treatment using nanotechnology are in pre-clinical phase of research. This review aims to summarize and highlight the developments and benefits of nanotechnology related to ocular devices, applied to the treatment of glaucoma, aiming to stimulate and accelerate research efforts in this area.

Methods of literature search

A systematic search was conducted at PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>) for English language articles, published until April 25, 2018. Key words used were as follows: “nanomedicine”, “nanotechnology” or “nanode-vices” and “glaucoma”, “glaucoma treatment” or “glaucoma surgery”. Matching study abstracts were reviewed and relevant articles were identified from the references. Fifty-six articles were included in this literature review.

Nanotechnology and topical treatment devices

New DDS with easy application, target delivery, sustained release and dose accuracy, associated to a lower rate of local and systemic side-effects are needed. Rapid drainage of topical eye drops and the consequent decrease in drug bioavailability justify the efforts of increasing drug residence time on the ocular surface, by either increasing formulations viscosity or creating systems that adsorb to the ocular surface (Tables 1 and 2).^{19,26,27}

The use of soft contact lenses (CL) as drug carriers for sustained drug release was an important step in the development of the DDS.²⁶ Mainly formed of hydrogel, soft CL present good ocular compatibility and may offer a longer and more controlled drug release profile. In addition, in the need of visual correction, improved visual acuity associated with ocular drug delivery may improve patients' therapeutic compliance.^{28,29} However, simple soaking the lens in a drug solution results in a short release-time of only 1–2 h, limited to the small amount of loaded drug and simple diffusion of low molecular weight and hydrophilic drugs.^{8,28} Another

possible drawback of simple soaking CL is the drug waste during storage. Nanoparticles are becoming effective vehicles for ocular delivery bioactive molecules. Entrapping the drug in nanoparticles before being dispersed by the CL matrix can further increase the amount of loaded drug, drug delivery and residence time on the ocular surface, as well as decrease waste during the storage period.^{17,19,30}

Thus, thermosensitive hydrogels promise to be efficient ocular DDS due to an easy drug encapsulation and administration. To design a CL resistant to drug release during packaging, Jung and Chauhan used high crosslinked nanoparticles of propoxylated glyceryl triacrylate (PGT) and ethylene glycol dimethacrylate, covalently linked to Timolol Maleate (TM) and then dispersed in hydroxymethylmethacrylate (HEMA) gels. Through a temperature-dependent mechanism triggered after contact with the ocular surface, TM was released for about 4 weeks. A temperature increase resulted in a higher amount of TM release and conversely, under refrigerated conditions, the majority of the loaded drug was retained on the CL. This suggests that the hydrolysis of the ester bond formed between TM and the nanoparticles could be acting as the rate-limiting step for TM release.³¹ Similarly, Jung et al. showed that a 5% particle loaded TM–PGT silicone hydrogel CL, was able to extend drug release at therapeutic rates for about a month at room temperature, with minimal impact on lens properties. In this study, the safety and efficacy of particle-loaded CL was also demonstrated by *in vivo* preliminary studies in Beagle dogs affected by or carriers of an hereditary form of primary open angle glaucoma.³²

In turn, Kim and colleagues demonstrated that nanodiamond clusters, embedded in enzyme-cleavable chitosan spheres and loaded with TM in a polyHEMA (pHEMA)

Table 1. Summary of nanotechnology-based contact lenses for ocular release of antiglaucomatous drugs.

Study	Lens structural matrix	Functional nanoparticle	Therapeutic agent	Results and remarks
Jung et al. (2012)	HEMA	PGT EGDMA	Timolol Maleate	Particle-loaded CL released TM in phosphate buffered saline for up to 4 weeks at therapeutic dose. Drug release may be dependent on ester bond hydrolysis between timolol and PGT/EGDMA, which is highly temperature sensitive. Under refrigerated conditions the majority of the drug loaded is retained in the lenses, whereas after an increase in temperature, drug release duration is reduced and the total amount of drug released is increased.
Jung et al. (2013)	Silicone	PGT	Timolol Maleate	Dispersing nanoparticles of PGT – timolol – PGT in a silicone CL, timolol can be delivered at therapeutic doses for about a month at room temperature, with a minimal impact on lens properties. Preliminary animal studies in Beagle dogs, demonstrated the safety and efficacy of particle-loaded CLs.
Kim et al. (2014)	HEMA	NDs coated with PEI-Chitosan	Timolol Maleate	NDs coated with PEI and cross-linked with an enzyme-cleavable polysaccharide–chitosan, were embedded within a CL polyHEMA matrix. TM release in the absence of lysozyme was undetectable. After contact with lysozyme, the cumulative drug release from the ND-nanogel lens was 9.41 µg in 24 h.
Maulvi et al. (2016)	HEMA	Ethyl cellulose	Timolol Maleate	A TM-ethylcellulose ring implant was developed and conjugated in a hydrogel CL under a sandwich system. <i>In vitro</i> kinetic release showed that 150 µg of TM loading dose presented a sustained drug release for 168 h, at therapeutic dose, with an excellent safety profile. <i>In vivo</i> studies in rabbit eyes showed a sustained IOP reduction for 192 h.
Metha et al. (2017–2)	Silicone	PVP PNIPAM	Timolol Maleate	Beaded double coating CL composed by electrically atomized formulations of TM, PVP and PNIPAM exhibit biphasic release profiles, with an initial burst followed by a sustained drug release. TM-loaded PNIPAM coating released most of the drug after 24 h, with an adequate ocular tolerability.
Sun et al. (2017)	PLGA-PEG-PLGA	LDH	Brimonidine Tartrate	Brimonidine loaded-LDH/Thermogel DDS containing 125.0 µg/g of Brimonidine showed a sustainable drug release for up to 144 h, with good corneal biocompatibility. This novel DDS significantly extended the drug release period and bioavailability compared to that from Brimonidine loaded LDH nanoparticles or commercial topical Brimonidine alone.

CL contact lens, DDS drug delivery system, EGDMA ethylene glycol dimethacrylate, IOP intraocular pressure, HEMA hydroxy methyl methacrylate, LDH layered double hydroxide, NDs nanodiamonds, PEI polyethyleneimine, PGT propoxylated glyceryl triacrylate, PLGA-PEG-PLGA poly-(DL-lactic acid co-glycolic acid)-polyethylene glycol-poly-(DL-lactic acid co-glycolic acid), PNIPAM polyisopropylacrylamide, PVP polyvinylpyrrolidone, TM Timolol Maleate.

Table 2. Other nanotechnology-based strategies for topical delivery of antiglaucomatous drugs.

Study	Nano-device	Functional nanoparticle	Therapeutic agent	Results and Remarks
Kashiwagi et al. (2013)	Nanosheet	Chitosan and sodium alginate	Latanoprost	A significantly and sustained IOP decrease for up to 6 days was obtained after a single application of the 40nm Latanoprost-loaded biodegradable nanosheet on the corneal surface, with an acceptable biocompatibility and security profiles.
Agban et al (2016)	Nanoshield	TiO ₂ ZnO ZnO/PVP	Pilocarpine Hydrochloride	ZnO/PVP nanoparticles cross-linked shields presented better cytotoxicity, transparency, mechanical strength, swelling capacity and bioadhesive profiles. Collagen shields cross-linked with ZnO/PVP nanoparticles released PHCI over a period of 14 days offering a promising sustained release system for glaucoma treatment.
Gagandee et al. (2013)	Nanopatch	PVA PCL	Timolol Maleate Dorzolamide Hydrochloride	Nano-fibers patch for conjunctival fornix application, avoiding corneal contact. <i>In vitro</i> release studies showed a controlled drug delivery for up to 24 hours, with an initial burst release, possibly attributed to the high surface area of the nanofibers, followed by controlled release of the drug from the nonofibers' core.
Jung and Chauhan (2013)	Fornix insert	PGT	Timolol Maleate	The 1-mm diameter, 7.5-mm long pHEMA loaded with 25% PGT-TM, released Timolol for about one week at a therapeutically effective dose. The release duration could be adjusted from 10 days to a month by increasing the fraction of nanoparticles in the insert. The mechanism of release is based on ester bond hydrolysis between Timolol and PGT.
Franca et al.	Fornix insert	Chitosan	Bimatoprost	Due to good biodegradable, biocompatible and mucoadhesive proprieties, chitosan-based ocular inserts were prepared for conjunctival fornix application as circular flexible membranes with 5 mm of diameter and about 50 µm of thickness loaded with 9.0 mg of Bimatoprost. After one application, the inserts sustainably released Bimatoprost <i>in vitro</i> during 8 h and IOP was significantly reduced for 4 weeks.

IOP intraocular pressure, PCL polycaprolactone,, PGT propoxylated glyceryl triacrylate, PHCI Pilocarpine hydrochloride, pHEMA poly hydroxyl ethyl methacrylate, PVA Polyvinyl alcohol, PVP polyvinylpyrrolidone, TiO₂ titanium dioxide, TM Timolol Maleate, ZnO zinc oxide.

hydrogel matrix, allow potent and reversible drug binding. This system enabled a controlled lysozyme-triggered drug delivery for 24 h once in contact with the lacrimal fluid and thus preventing drug waste while CL are stored in storage solutions.¹⁷ On the other hand, Maulvi et al. combined a ring of TM-loaded ethylcellulose nanoparticles with a soft CL under a “sandwich system”. The resultant combination showed sustained drug release and IOP reduction, at therapeutic dose, for 8 days in rabbit eyes, without affecting CL optical and physical properties. This system also presented a good profile in terms of biocompatibility and drug maintenance during the storage period.³³

In a recent study, Metha et al. developed an on-demand nanostructured multiple coating CL, composed by electrically atomized formulations of TM, polyvinylpyrrolidone (PVP) and polynisopropylacrylamide (PNIPAM). This beaded morphology coating CL showed an *in vitro* initial fast release of TM, due to fast dissolving PVP, followed by a more sustained drug release after 24 h, due to slower dissolving PNIPAM. Once again an adequate ocular tolerability was registered during the study period.³⁴ In order to overcome the poor bioavailability of ophthalmic drugs, the same group demonstrated that the use of different permeation enhancers (PE), such as benzalkonium chloride, ethylenediaminetetraacetic acid, Borneol and Brij® 78, resulted in different release profiles, increased drug absorption and intra-ocular bioavailability. In addition, the use of PE slowed down the initial burst release of TM, with a higher increment in the amount of drug released after 24 h.³⁵ Finally, Sun et al. designed a double layer hydroxide (LDH)/soft thermogel LC as a DDS for topical release of Brimonidine Tartrate. Upon contact with the tear film, Brimonidine was released from LDH nanoparticles to the thermogel matrix and then to lacrimal fluid, resulting in an effective drug concentration in the AH for at least 7 days and a sustainable IOP reduction for up to 4 days.³⁶

In an attempt to develop a novel DDS applied to the cornea, avoiding the potential CL-related drawbacks, such as foreign body sensation and ocular surface inflammation, Kashiwagi et al. developed a 40 nm thick Latanoprost-loaded, multilayered biodegradable nanosheet, composed of chitosan and sodium alginate, by a layer-by-layer method. With an identical efficacy of commercial 0.005% topical Latanoprost, this novel DDS reduced IOP for approximately 1 week without producing any severe side-effects. The degradation of this nanosheet was observed *in vitro* in phosphate buffered saline after approximately 10 days.³⁷ On the other hand, Agban and colleagues created a nanoparticle cross-linked collagen shield to be placed on the cornea, for pilocarpine hydrochloride topical delivery, using a solvent casting method. Metal oxide nanoparticles of titanium dioxide (TiO₂), zinc oxide (ZnO) and PVP capped ZnO (ZnO/PVP) were used as cross-linking agents. The ZnO/PVP nanoparticles presented the best results in terms of cytotoxicity, transparency and tensile strength. It exhibited a rapid release of surface bound zinc ions during the first day, followed by a constant drug release for nine days due to the diffusion of ions linked to the collagen matrix. Additional cross-linking with UV light slowed drug release rate to over 14 days.³⁸

In a different way, Gagandee and colleagues designed a biodegradable patch made of polyvinyl alcohol and polycaprolactone nanofibers, using an electrospinning technique, loaded with TM and Dorzolamide Hydrochloride. The nanopatch was designed for fornix placement, avoiding visual disturbances and ocular discomfort, showing good biodegradable and biocompatible profiles. *In vitro* studies revealed a controlled drug release up to 24 h. *In vivo* studies, in rabbit eyes, showed a significant and constant IOP reduction, resulting in an extended therapeutic activity up to 72 h.²³ In turn, Jung and Chauhan developed an insert of about 7.5 mm in length and 1 mm in diameter also to be applied in the conjunctival fornix, prepared by through the incorporation of TM-loaded nanoparticles of PGT into a p-HEMA matrix. Timolol was released for about 10 days at a therapeutically active rate. To minimize drug loss during the storage period, the authors advised to maintain the insert in a dry state and its hydration

before placement in the *cul-de-sac*.³⁹ Similarly, Franca et al. created a chitosan polymeric ocular insert for sustained release of Bimatoprost in the conjunctival fornix, which resulted in an *in vitro* drug release for 8 h and a significant IOP reduction for 4 weeks, after a single application.⁴⁰

Surgical devices

When it comes to glaucoma surgery, researches in the field of nanotechnology have also brought promising results.

GDD have been traditionally indicated in cases of high-risk glaucomatous eyes for failure of standard filtering surgery.⁴¹ Despite some differences in terms of their surface area, shape, composition including valved or nonvalved profile, the main GDD available in current practice present similar overall success rates in controlling IOP as well as a significant number of postoperative complications. Hypotony due to excessive AH drainage, is a relevant early postoperative complication, especially in nonvalved devices. On the other hand, fibrosis around the drainage plate still continues to compromise the long-term success of all GDD, accounting for almost 50% of failure rates at 5-year post-surgery. Research efforts were made to develop more physiologic, inert biomaterials and innovative systems to minimize these complications (Table 3).^{41–44}

To overcome postoperative hypotony of nonvalved GDD, Maleki et al. fabricated a truncated-cone-shaped plug filter, designed to be inserted into the silicone tube of a Baerveldt® implant. Biodegradable polymers of polylactic-co-glycolic acid (PLGA) and poly-lactic-acid (PLA), which complete degradation once wound healing has progressed through the hypotony phase were used. The resultant plug filters presented 500 µm long, with a 500 µm diameter base, a 300 µm diameter

apex and a 44 µm diameter hole in the center. *In vitro* studies revealed that the 50/50 PLGA/PLA plug filters coated with SU-8 or UV-curing adhesive were able to control IOP for up to 45 days, however with a sharp pressure drop once plug filter degraded.⁴² In turn, Olson and colleagues designed a GDD regulator also aiming a controlled and sustained AH drainage. In order to achieve their goal, the group adapted a regular 23-gauge silicone tube from a traditional GDD, to present a 45° beveled extremity, covered by a polyvinylidene fluoride nanopore membrane. The tube must be placed beneath a traditional trabeculectomy flap, through a sclerostomy, placing the beveled extremity into the anterior chamber (AC) and its other extremity fixed to the sclera, to prevent tube migration. In the postoperative period, the nanopore membrane can be ruptured thorough a Nd:YAG laser beam, enabling the adjustment of AH drainage, if indicated.⁴⁵

Paschalis et al. designed a ferromagnetic-valved tube for IOP control independent of subconjunctival encapsulation, based on pressure-sensitive ferrofluidic nanoparticles. The ferrofluid nanoparticles of Fe₃O₄ suspended in fluorocarbon carrier oil exhibit superparamagnetic properties, such as drag force along a gradient field. With two rare earth micro magnets the valves were calibrated to open at 10 mmHg and close at 7 mmHg, enabling a linear and highly predictable IOP control. *In vivo* preliminary studies in rabbit eyes, demonstrated good biocompatibility and tolerability, with a significant lower IOP compared to contralateral control eyes, within 2 weeks of surgery.⁴⁶

Following a somewhat different research pathway, Pan et al. developed an artificial nanodrainage device – ANDI, with 1.5 mm diameter and 4 mm length, fabricated through microelectromechanical systems (MEMS) and nanofabrication technologies. It consists of a nanoporous membrane,

Table 3. Summary of nanotechnology-based drainage devices.

Study	Device	Functional nanoparticle	Results and remarks
Maleki et al. (2012)	Plug filter	PLGA PLA	The biodegradable truncated-cone-shaped plug filter made of 50/50 PLGA coated with SU-8 or UV-curing adhesive was able to control IOP for up to 45 days. However, the bulk degradation of PLGA, resulted in a sharp drop in IOP.
Olson et al. (2015)	Nanopore membrane	PVDF	A nanopore membrane of PVDF was developed, serving as a glaucoma drainage device regulator. An <i>ex vivo</i> increase of Nd:YAG laser perforations, increased in AH outflow.
Paschalis et al. (2013)	Ferromagnetic valved tube	Fe ₃ O ₄	Valve's opening and closing pressures were calibrated at 10 and 7 mmHg, respectively. Pressure calibration was maintained over the entire experiment's duration (3 months) with small variations in IOP of less than 0.5 mmHg. Preliminary <i>in vivo</i> results suggest that the valve has good biocompatibility and is able to control of IOP in rabbit eyes.
Pan et al. (2006)	ANDI	PMMA	The nanoporous glaucoma implant provided flow resistance to saline flow, while cross-linking and clogging of proteins inside the nanopores from plasma perfusion, significantly increasing the flow resistance.
Harake et al. (2015)	Micro-shunt	PEG PET	<i>In vitro</i> flow studies showed a pressure drop around 10 mmHg, a continuous long-term stability through 10 day on protein flow testing and good safety profile against infection from bacterial ingestion.
Sahiner et al. (2009)	Drug-coated glaucoma drainage Device	pHEMA	Semicircular pHEMA disks loaded with MMC ((0.17, 0.35, and 0.8 mg/g of dry gel) were attached to the lower half of an Ahmed glaucoma valve® plate, releasing MMC <i>in vitro</i> for 1–2 weeks. All the MMC was released from the disks <i>in vivo</i> during the 3 months of the study. Histologic analysis revealed a significant reduction in blebs' inflammatory reaction and fibrosis, without differences among the three different concentrations of MMC.
Ponnusamy et al. (2014)	Drug-coated glaucoma drainage Device	PLGA	A double-layered coated Ahmed valve®, provided a burst of MMC release followed by a slow release of 5-FU, in order to prevent fibrosis over 28 days, representing the most active period of postoperative wound healing.

5-FU 5-fluorouracil, ANDI Artificial Nano-Drainage Implant, IOP intraocular pressure, MMC mitomycin C, Nd:YAG neodymium-doped yttrium aluminum garnet, PEG Polyethylene glycol, PET Polyethylene terephthalate, pHEMA poly(2-hydroxyethyl methacrylate), PLA poly-lactic-acid, PLGA polylactic-co-glycolic acid, PMMA polymethyl methacrylate, PVDF polyvinylidene fluoride.

with a set of pores, a top opening of 400 nm and a bottom opening of 200 nm in diameter connected to an integrated polymeric shaft. Its design allows an insertion through the sclera into the AC, creating a bypass of AH from the AC to the subconjunctival space.⁴⁷

Harake et al. created an implantable MEMS microfluidic device, formed of parallel micro-channels of polyethylene glycol (PEG) 214 and PEG 4000, to provide stability against swelling and resistance to channel clogging from biofouling. To create a support layer, it was conjugated with polyethylene terephthalate, increasing the mechanical stiffness and durability of the device. It was also designed to be inserted through the sclera, as a minimally invasive surgery, enabling AH outflow from the AC to the tear film, resulting in a stable mean IOP decrease of 10 mmHg during the entire experimental period. Additionally, the device revealed to be resistant to bacterial intrusion.⁴⁸

Despite the lack of prior evidence supporting the use of antifibrotic agents in GDD surgery, such as Mitomycin C (MMC) and 5-Fluorouracil (5-FU), it seems that repeated bleb injections with these drugs decrease surgical failure by decreasing the hypertensive phase and subconjunctival fibrosis.⁴⁹ However, taking into account the inconvenience of repeated bleb injections, such aggressive postoperative manipulation could be overcome by pre-coating the GDD with antifibrotic agents prior to implantation.^{50,51} Sahiner et al. created a slow-release antifibrotic drug-coated GDD, incorporating MMC in pHEMA disks, which were then attached to a commercial Ahmed valve® plate. The resulting device released MMC *in vitro* over 1–2 weeks and for up to 3 months in rabbit eyes, with a significant decrease in bleb inflammatory reaction and fibrosis.⁵² Similarly, Ponnusamy et al. designed a drug-coated Ahmed valve®, using biodegradable PLGA in a double-layered film arrangement. 5-FU was dispersed into the bottom layer with MMC surface loading to the top layer. This drug-coated Ahmed valve® presented an overall antifibrotic activity for up to 4 weeks, characterized by a burst release of MMC followed by a slow release of 5-FU.⁵³

Still within the field of glaucoma surgery, Lambert et al. synthesized a biodegradable polyester nanosponge (NS) as a DDS for Brimonidine, Bimatoprost or Travoprost intraocular delivery via intravitreal injection. *In vivo* studies in mice eyes concluded that a single injection of the NS could effectively deliver hypotensive drugs in a linear and continuous manner for up to 32 days. Moreover, this could be an effective method for delivering neuroprotective agents to retinal ganglion cells, since intravitreal injection of a NS loaded with Neuro-DiO dye led to the internalization of the dye by those cells.⁵⁴

Finally, a single intracameral injection of low-dose of ENV515 – Travaprost (Envisia Therapeutics), the only DDS-based on nanotechnology in phase 2 trial, decrease IOP by 6.7 mmHg over 11 months, with a good safety profile.

Conclusion

Nanotechnology has brought promising benefits for the treatment of glaucoma. New DDS, intrinsically connected

to health care and engineering sciences, with advantageous profiles in drug delivery, bioavailability and biocompatibility may change the paradigm of health services. Indeed, nanotechnology seems to provide valid options to answer the unmet needs in glaucoma management, ranging from an improvement in drug bioavailability to the promotion of an improved surgical efficacy and safety profile. However, it is important to remind that, despite revealing promising results, published data are obtained mainly from *in vitro* and animal studies. In fact, the majority of the devices here discussed are still in the research or development stage and ENV515 is the only DDS using nanotechnology in phase 2 trial.²⁵

In summary, while ocular devices for the treatment of glaucoma based on nanotechnology are widely expected to continue to develop, it is still not possible to estimate how close their use to daily clinical practice. More efforts are needed in order to prove the biological consequences, efficacy and safety of nanotechnology treatment approaches in human eyes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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