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Nanomedicine for ophthalmology: potential therapeutic approaches

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The study of nanotechnology has ushered in a new era in medical science in recent years. The term 'nano' refers to the nanoscale particle spectrum that includes cellular and molecular structures and is usually between 10 and 1,000 nm in size. Nanoparticles have several advantages over conventional ophthalmic medications including abilities of smart drug targeting; extended drug release time; have reduced toxic effects; and use of gene therapy. After a quick introduction to nanoparticle classification, we'll concentrate on the potential uses of various nanoparticles in the treatment and detection of various retinal pathologies and present cutting-edge nano-derived methodologies.

Keywords: *Nanoparticles, ocular disease, drug delivery, medicine*

INTRODUCTION

The basis for various medical uses of nanomaterials was established by the creation of materials, structures, processes, and equipment on the scale of cellular and molecular structures and in the range of 1-1000 nanometers. Nanomedicine is a branch of science that uses nanotechnology to diagnose and treat various illnesses. It offers important insights that are advancing modern healthcare. The development of nanotechnology, in particular, looks set to significantly accelerate progress in ophthalmology.

To treat a wide variety of retinal pathologies including retinal degenerations, retinopathy, Retinitis pigmentosa and uveitis, researchers have developed nanomedical agents in varied shapes, including hydrogels, liposomes, dendrimers, nanoemulsions and nanospheres (Sharma and Sharma, 2021). The permeability of therapeutic molecules as well as advancements in their biodistribution and bioavailability has all been thoroughly investigated in recent years to address the problematic accessibility of different medications to the corneal and aqueous barriers as well as the inner and exterior blood-retinal and blood-ocular barriers. Drug targeting, regulated release, and penetration can all be improved with nanoparticles.

Moreover, it has been demonstrated in numerous studies that the use of nanoparticles increases the therapeutic efficacy of medications for ocular diseases. The use of some of these therapeutic nanoparticles for treating ocular diseases has been addressed in the sections that follow, along with a summary of their applications and a list of important factors to consider.

Nanomedicine

By manipulating nanomaterials, the science of nanotechnology studies, creates, operates and

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uses functional materials, tools and systems (1–100 nm). Nanotechnology is being used more and more in the diagnosis, treatment and management of different diseases. Nanomedicine is the name of this novel scientific discipline. The use of nanotechnology in ophthalmology has advanced along with advances in health and surgery. To maximize drug bioavailability, increase the time spent in contact with the eye and lessen the need for eye removal, novel eye nano-systems with various shapes and properties have been developed (Chaudhary and Mishra, 2022). Numerous nano-systems have been used in the management of numerous eye disorders. For the treatment of xerophthalmia, biodegradable subconjunctival implants, nanoparticle-filled contact lenses with acetazolamide, diclofenac eye-release nanocolloid systems based on hydrogel, polymer nanocolloid systems for inflammatory diseases and nanostructured lipid transporters for managing drug delivery in ocular infections are just a few examples.

For the delivery of ophthalmic drugs, various nanoscale materials have been created with particular properties. Numerous nanosystems exist, such as dry eye syndrome-specific nano-based subconjunctival implants, nanomicelle-based polymers, glaucoma-targeted nanoparticle-loaded contact and hydrogel-based polymers. Additionally, numerous varied kinds of nanoparticles are being extensively researched for the sustainable and nontoxic delivery of various medicines into the ocular system (Romanowski et al., 2016). Regardless of all the advances in nano-based drug delivery systems, most of the nanosystems listed above are still at the experimental stage

Nanomicelles are the most popular methods for delivering ophthalmic medications to the anterior and posterior eye regions. Amphoteric compounds can quickly and easily create self-assembling nanomicelles. Nanomicelles could be considered to be safer than other types of nanomaterials because fewer auxiliary materials are required in their production. Due to the hydrophobic core, hydrophobic agents easily dissolve and result in a clear aqueous formulation when ready for administration to the posterior and anterior segments of the eye.

For instance, nanomicelle-based dexamethasone that was delivered to the anterior segment of the eye demonstrated greater bioavailability than the suspension of dexamethasone (Swaminathan, Vavia, et al., 2013). Additionally, therapeutic agents are easily delivered to the eye's posterior region by stable nanomicelles (Terreni et al., 2021). For the treatment of various ocular diseases, nanomicelles containing various medications, such as rapamycin, have been created recently (Wei et al., 2018).

One of the most preferable dendrimers for ocular agents' delivery is poly(amidoamine) (PAMAM) (Qin et al., 2020). Due to suitable biodistribution and adaptable structure in different ocular segments, dendrimers have proven to be one of the most useful drug delivery systems at the nanoscale.

It has been claimed that encapsulating fluoroquinolones like nadifloxacin and prulifloxacin within PAMAM dendrimers increase the antibacterial potency of the drugs relative to free drugs (Kamaleddin, 2017).

Dendrimers may be applied as eye topical drops that can sustain the delivery of antimicrobial agents on the cornea's surface without affecting visual creation. PAMAM dendrimers have also been successfully used in rabbit ocular systems to deliver glucosamine, tropicamide, and pilocarpine nitrate. One of the concerns about the selective delivery of dendrimers to ganglion cells of the retina is toxicity and inflammation.

Delivery of nano-drug from retinal-blood barrier

Water and small, water-soluble compounds can cross the inner BRB (iBRB) via paracellular transport, which is controlled by the dynamic opening and closing of complex junctional protein complexes that connect and seal two adjacent retinal microvascular endothelial cells RMECs. These complexes are typically smaller than 3 nm in radius and around 500 Da. Several functional classes of junctions, including tight junctions, adherens junctions and gap junctions make up these protein units.

Collectively, they control Microvascular endothelial cells (EC) growth inhibition and cell-to-cell adhesion, preserving cell polarity and

survival, and eventually regulating paracellular permeability. EC connections commonly entangle with one another to generate even more complicated junctional proteins, in contrast to epithelial cells, which typically have each set of their junctions as independent entities. For example, in RMECs, tight junctions frequently form higher structural protein complexes with adherens junctions and gap junctions, which is consistent with their role in arbitrarily limiting paracellular transport.

Certain medications, especially those with greater molecular weights, are unable to reach the retina in sufficient amounts because of the blood-retinal barrier's reduced permeability (Wang and Pang, 2023). The blood-retinal barrier works as a discriminating blocker between the circulatory and nervous systems assisting in preserving equilibrium throughout the retina. The interior dynamic structure of the blood-retinal barrier is organized by astrocytes, pericytes, endothelial cells and the outer blood-retinal barrier is the tight junction shaped by the retina's pigment epithelium cells (Wang and Pang, 2023).

Gold nanoparticles with a diameter of nearly twenty nm have been demonstrated to penetrate through the blood-retinal barrier and distributed throughout the retina's layers with minimal (if any) negative impacts on the survival of astrocytes and retinal endothelial cells (Masse et al., 2019).

Earlier research revealed that there is no place in the retina where 100 nm particles can be found, indicating the preferential impact of NPs' size when passing the blood-retinal barrier. The fact that these NPs have no toxic effects on the retinal structures or functional abnormalities was also further supported by histological investigations. It's important to note that surface chemistry can have an impact on how Nanoparticles are distributed. Positively charged nanoparticles can bind to the nearby anionic vitreous elements.

Anionic nanoparticles, on the other hand, are discovered to diffuse through the vitreous and enter the layers of the retina. Furthermore, there is no conclusive proof that the administration of gold nanoparticles has altered the expression or structure of any characteristics of biological molecules. These findings imply that gold nanoparticles are a viable alternative and have excellent *in vivo* applicability for the blood-retinal barrier's delivery of drugs (Lohia et al., 2022).

Nano-based therapeutic strategies

Because of immediate exposure of the cornea to the environment, it is vulnerable to a variety of diseases. The general circulation and the body's immune system are practically cut off from the cornea, making it easily available. In gene therapy, the transport of the desired genes to the cornea or nearby tissues is the prime option for gene therapy.

Better sustained delivery and transfection efficiencies provided by nanoparticles-based gene therapy are made possible by the improved uptake in cells, endosomal crossing and carriage capability to the nucleus. Corneal gene therapy has been effectively used in recent preclinical studies to stop herpetic stromal keratitis, neovascularization and rejection of cornea in animal models, nanoparticle intrastromal injection is a suitable technique for ocular gene therapy (Di Iorio et al., 2019).

For example, an anti-VEGF cassette expressing a short hairpin RNA with PLGA nanoparticles injected intrastromal inside of plasmid to treat corneal neovascularization. As a result of its immunosuppressive impact, anti-VEGF factors were also tried for delivery via subconjunctival injections to prevent murine cornea transplant rejection (Swetledge et al., 2021).

Keratitis, conjunctivitis and uveitis are the diseases that correlate to the inflammation of the uveal tissues, conjunctiva and cornea respectively. Nanoparticles have a greater bioavailability, longer residence time and longer duration of effect making them a potential treatment for uveitis. For instance, immunologic responses to nanoparticles containing betamethasone phosphate in rats with experimental autoimmune uveoretinitis were inhibited.

Accordingly, nanoparticles coated with tamoxifen and encapsulating betamethasone have shown anti-inflammatory benefits in instances of uveitis. The peptide is conjugated with the poly(ethylene glycol) (PEG)-coated nanoparticles for ocular administration. Nanoparticles coated with PEG for tamoxifen delivery showed the prohibitory impact on inflammation in experimental autoimmune uveoretinitis rats

(Bhuwane et al., 2022). These findings back up the earlier assertion that therapeutic agents enclosed in nanoparticles have greater bioavailability and efficacy. Fungal keratitis in rabbits has been treated with chitosan hydrogels, which have been revealed to improve maintenance time. Encapsulated nanoparticles also enhanced therapeutic effects, prolonged antimicrobial activity in contact lenses and showed sustained release in keratitis models (Chang et al., 2022).

Any damage to the cornea's cutaneous tissue will significantly impair eyesight. Suturing the eye is a common clinical procedure for corneal wound healing but it comes with several risks including infections, astigmatism, corneal scarring and postoperative cataracts. To lessen the drawbacks, various adhesives and polymer glues have been used but almost none of them have produced perfect results. Highly branched nanostructured dendrimer-based hydrogels were able to support wound healing quickly without scarring or inflammation because of their carefully controlled crosslink networks (Wang et al., 2021).

Additionally, crosslinker modifications altered adhesive degradation time which allows for exact control of the time it takes for wounds to heal. Fresh blood vessels develop inside the normally avascular corneal tissue as a result of the pathological condition known as corneal neovascularization, which is typically accompanied by inflammation, infection and traumatic or degenerative illnesses. Different treatments for corneal neovascularization aim to stop angiogenesis by blocking angiogenic factors (Shen et al., 2022). According to research, PLGA nanoparticles containing short hairpin RNA-containing plasmid are extra efficient against VEGF than bare plasmid (Zhang et al., 2010). Additionally, copolymer and plasmid DNA conjugated in nanomicelles that produce soluble VEGF receptor-1 was applied in gene therapy methods to block the signaling pathway of angiogenesis (Kanazawa et al., 2012).

Choroidal neovascularization (CNV), caused by the expansion of vessels choroid under the epithelium of the retina, causes hemorrhage and scarring. Nanomedicines are founded effective in inhibiting additional angiogenesis, similar to how corneal neovascularization is treated. Dexamethasone acetate is shown to discharge under controlled conditions when enclosed in PLGA nanoparticles, which results in preventing impacts on CNV (Xu et al., 2007).

It has been suggested that poly (lactic acid/poly (ethylene oxide)) nanoparticles significantly suppress CNV and have a longer effect in the form of encapsulation (Heald et al., 2002). Using PLGA/chitosan nanoparticles, the proteolytic plasminogen kringle 5 plasmid enclosed and injected intravitreally (Abd et al., 2018).

The effectiveness of nanoparticles in inhibiting VEGF production has also been demonstrated by the use of encapsulation of small interfering RNA in PEGylated liposome protamine hyaluronic acid nanoparticles. Additionally, previous works showed that anti-VEGF plasmids enclosed in PLGA NPs can effectively reduce CNV through targeted delivery. By using the proper nanocapsules for targeted drug administration, anti-angiogenic medications are no longer inaccessible to the retina and subretinal spaces. Additionally, polyion complex micelles with 10 nm were used to deliver drugs for the successful treatment of CNV (Wang et al., 2009).

Another study has proposed using photodynamic therapy to treat neovascular disease using supramolecular nanocarriers loaded dendritic photosensitizers. The structure prevents the core sensitizer from aggregating which triggers a photochemical reaction that obstructs CNVs notably effectively while causing the least amount of unfavorable phototoxicity.

Elevated intraocular pressure (IOP) is a common symptom of glaucoma (ganglion cells of the retina gradually degenerate). Glaucoma is one of the major global causes of blindness. In the treatment of glaucoma, the goal is to decrease the pressure on the eyes either increasing or reducing aqueous humor production. By quantum dots monitoring and observing after injection into the ocular system, it may be possible to determine how the lymphatic of the eyes contributes to the drainage of liquids from the eye (Tam et al., 2011).

Timolol and brimonidine are two prevalent therapeutic drugs that have been delivered to the eye using various nanoscale structures with

improved sustained delivery and bioavailability. Similarly, by encapsulating and administering thermal shock proteins or glial cell line-derived neurotrophic factor, it is possible to regenerate damaged neuronal cells (Bigdeli et al., 2023).

Nanotechnology for Retinal Diseases Diagnosis

Recently nanoparticles have been created as agents to boost imaging contrast in techniques including CT, X-ray and fluoroscopy. The amphiphilic cyanine dye indocyanine green (ICG) was approved by Food and Drug Administration for therapeutic use in 1954 (Haritoglou et al., 2012). ICG's limitations on the detection of retinal disorders including its reduced hydrolytic stability and little photo restrict ICG's potential usage (Haritoglou et al., 2012). It appears that one way to get around these limitations is to incorporate ICG into nanoparticle systems. To increase contrast, ICG enclosed in nanoparticles can be applied for imaging including photoacoustic and near-infrared (Haritoglou et al., 2012).

Since they can absorb NIR radiation gold nanoparticles have attracted attention as potential contrasting agents. This allows for discriminating visualization with little noise in the background. OCT imaging has improved thanks to gold nanoparticles. Previous work showed injecting Au NPs into mice's retinas to enhance contrast and significantly improve the clarity of scanned lesions (Hainfeld et al., 2006).

Au NPs were used to enhance the monitoring of transplanted photoreceptor precursors (PRPs), and after a month there were no negative side effects (Betzer et al., 2020). Chain-like Au nanoparticles were introduced that increased the OCT signal by up to 176% (Paulus et al., 2020). Peptide-functionalized silicon nanoparticles (SiNPs) were created to label angiogenesis and inhibit neovascularization having a dual impact (Dougherty et al., 2015).

Human embryonic stem cell (hESC) or induced pluripotent stem cell (iPSC)-derived RPE cell transplantation has demonstrated revolutionary results in eye illnesses (Singh et al., 2019). To maximize the functional advantages of cell therapy deep learning of the biodistribution and survival of transplanted cells is required. Magnetic nanoparticles primarily iron oxide nanoparticles have the ability for 3 months labeling in magnetic resonance imaging (MRI) and this labeling has no impact on the precursors' capacity to differentiate, proliferate or stay viable (Giannaccini et al., 2017).

The stable magnetic properties and characteristics of carbon materials of the carbonized CM and CMT NPs allowed the nanoparticles to accomplish imaging simultaneously. Magnetic nanoparticles can deliver medications to the body through a variety of methods including intravenous infusion and topical application and they can be guided to particular body locations by magnetic fields. In one research magnetic nanoparticles and nerve growth factors were covalently coupled and controlled magnetic fields were used to transport the magnetic nanoparticle complexes to the retina (Giannaccini et al., 2017).

Poly (3,4-ethylenedioxythiophene) (PEDOT)/ gold nanocomposites have proven to be a reliable and accurate method for VEGF concentration measurement. To increase the binding of PEDOT to antibodies, PEDOT/gold nanocomposites were created. They discovered that over a range resistance of the charge transfer remained linearly linked with the concentration of the analyte's VEGF. The level of the retina's VEGF can be determined in this manner to increase the detection precision and exactly regulate the frequency and dosage of injections of antiVEGF medications. Both of cost and the adverse effects of an overdose of anti-VEGF medications can be significantly reduced with accurate VEGF concentration measurement (Kim Jr et al., 2019).

Nanomedicine and toxicity

The biocompatibility of NPs should be taken into consideration for ophthalmic therapeutics application, and biomedical administration of nanoparticles shouldn't result in genotoxicity, cytotoxicity, or any type of immunological reaction. The retina which contains numerous neuronal cells may be a possible target of the neurotoxicity of nanoparticles. In turn, the possible ability of nanoparticles to penetrate the blood-brain barrier by increased distribution in the layers of the retina could make NPs more toxic by

increasing their toxicity. Different toxicology tests should be conducted in conjunction with novel forthcoming carriers taking into account the potential side effects of nanoparticles (Khiev et al., 2021).

Multiple investigations have looked into the potential neuronal toxicity of nanoparticles. One of these processes with the most support is reactive oxygen species overproduction. For example, titanium dioxide (TiO_2) nanoparticles perturbed the electricity activation in a network of neurons by causing intracellular reactive oxygen species production in glial and neurons (Wu and Tang, 2018). Additionally, after being exposed to silica NPs, microglial cells displayed phagocytic behavior and took them up, which increased the generation of reactive nitrogen species and intracellular ROS (Wu and Tang, 2018). Furthermore, the epithelium of retina pigments and cells of the epithelial lens have shown increased cytotoxicity and phototoxicity after receiving hydroxylated fullerene nanoparticles (Wielgus et al., 2010).

Nanomedicine and regenerative ophthalmology

There are two areas of tissue engineering research. Additive tissue engineering, of them, substitutes cells or tissue attempts to replace missing tissue by growing new tissue. The other, called arrestive tissue engineering, seeks to halt unnatural development. Depending on the target, medicinal nanodelivery can have either an additive or an arrestive effect on the environment. The distribution and pace of healing can be manipulated by altering the environment at the nanoscale. Together, there are a huge number of procedures that could benefit from nano-based engineering in retinal diseases such as tests to determine whether retinal ganglion cells are still viable, cell transplantation of endothelial cornea and cell repair of retina ganglions the nanofiber-based scaffold construction and gene therapy to prevent neovascularization in intraocular tissue (Hunt et al., 2018).

In recent years a framework for delivering ocular therapeutics has been created. Particularly nanosystems have been developed for the transport of hydrophilic and lipophilic medications. For instance, polynucleotides on the polysaccharide chitosan meet the needs of the topical ocular pathway (Hunt et al., 2018).

One significant issue in neuromedicine - the inability of nerves to reinstate neural tasks - has prompted researchers to investigate whether nanotools and nanomaterials can be applied. The creation of novel nano-bio-based scaffolds that act as ducts and promote regrowth is one potential solution. Another is the application of new nanoscale surgical tools for functional axon repair and surgical micro-splicing (Karamichos, 2015).

The use of novel tissue scaffold materials and architectural designs has improved regeneration, and straight restoration of nerves in individual axons and neurons has been made possible thanks to nanoscale technologies. Because of the use of nanotechnology in ophthalmology, new approaches to treating ocular diseases have been developed that can get past ocular obstacles and have a longer-lasting effect on the target tissues. For example, using eco-friendly scaffolds to transport progenitor cells of the retina for restoring the injured ocular system is a promising treatment for eye diseases.

CONCLUSION

In conclusion, nanomedicine can help with gene therapy, increase bioavailability, exact delivery, constant release and offer novel diagnostic and therapeutic methods nanoparticles are an effective instrument opening up novel possibilities for the identification and management of the majority of ophthalmological pathologies.

There are still many problems to be resolved, though, because most NP research is still in the trial stage and only a small number of them are used in clinical settings. For instance, some nanoparticles including silver, zinc sulfide and titanium dioxide, have dose/size-related toxicity that restricts their usage in ophthalmology. It is critical to be mindful of the risks posed by nanoparticles including cytotoxicity to the eyes. In conclusion, more studies will improve the development of nanoparticles and the retina is a promising application area for nanomaterials.

Declaration of competing interest

The authors declare no competing interests.

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