

Nanoparticles in Ophthalmology

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Abstract

For about 20 years, nanotechnological applications are intensively investigated in all fields of medicine. In ophthalmology, nanoparticles are of special interest as carrier systems for the targeted delivery of drugs, genes or siRNA to the anterior as well as to the posterior segment of the eye. Above that, sustained drug release plays a major role for the treatment of many ophthalmic diseases and nanoparticles have the potential to perform this task without inducing local adverse reactions.

Nanoparticles are primarily defined by their size that has to range below 100 nm. All other characteristics are variable. The large variety of nanoparticle types and the fact, that they are easily modifiable allows their adaption to the task set for them.

In this review, we summarize the application of nanoparticles in ophthalmology and describe the current challenges.

Keywords: Drug delivery, Nanoparticles, Nanomedicine, Nanotechnology, Ophthalmology

Introduction

The targeted delivery of therapeutic drugs in sufficient quantity to their desired site of action has been a challenge ever since, especially to organs and/or parts of the body with drug delivery barriers. For example, while the skin is easily accessible from the outside, other organs/tissues, due to their location, are only accessible via systemic drugs through the vascular system. The brain is further restricted by the blood brain barrier.

The eye is actually quite accessible for therapeutic interventions regarding its localization in the body. However, it is equally protected by numerous physical and physiological barriers. Among these barriers are the tear film barrier, the corneal barrier, the con-

junctival barrier, the scleral barrier as well as the blood aqueous barrier (BAB) and the blood retina barrier (BRB). On the one hand, these barriers protect the eye from being harmed by microorganisms, toxins or other substances. On the other hand, these barriers complicate drug delivery to the eye [1,2].

The traditional ways used to deliver therapeutic drugs to the eye are shown in Figure 1. The two main ways are local and systemic administration. Local administration can either be performed by topical administration or via periocular (subconjunctival, subtenon, posterior juxtасcleral, retrobulbar, peribulbar) or intravitreal injections [1].

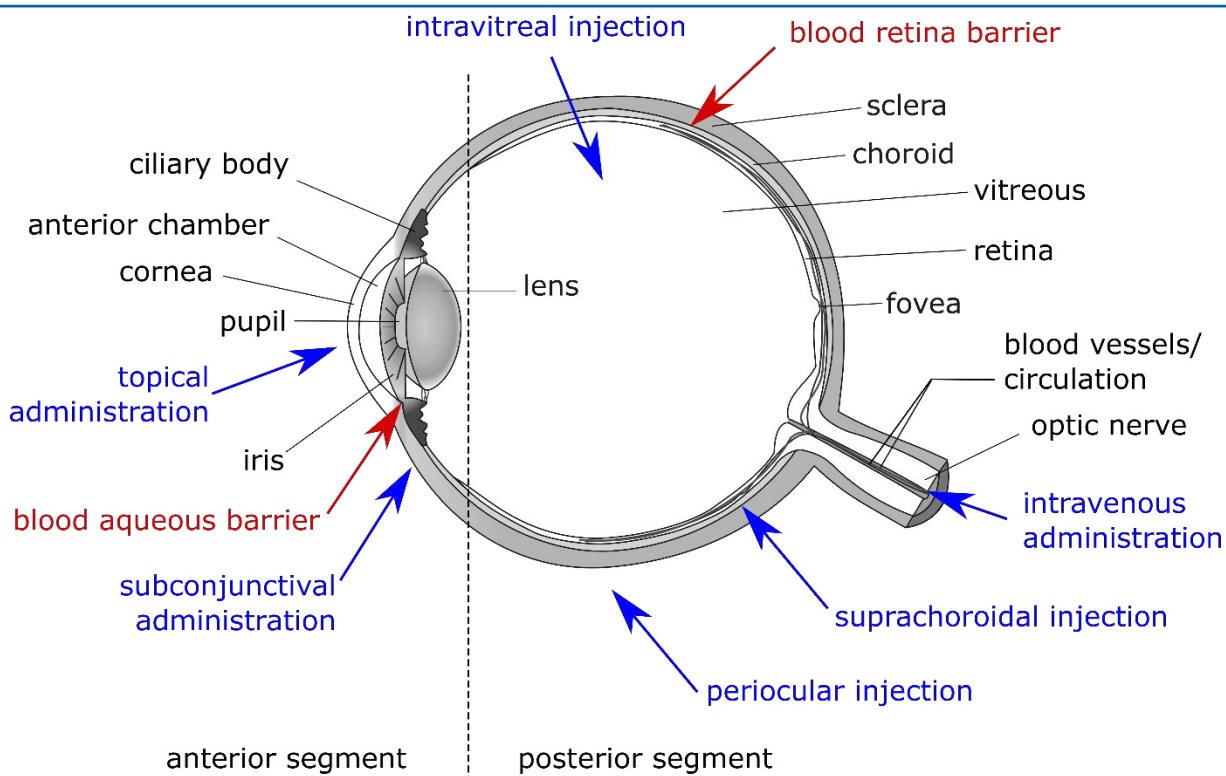


Figure 1: Structure of the eye and conventional routes of drug administration. The eye can be divided into anterior and posterior segment. The anterior segment consists of the cornea, the conjunctiva, the anterior chamber, the iris, the pupil, the ciliary body and the lens. The cornea (including the tear film) and the blood aqueous barrier pose limits for drug delivery to the anterior segment. The majority of drugs is delivered by topical administration via eye drops or ointments. The posterior segment consists of the vitreous, the retina, the choroid and the optic disc. Drugs can be delivered by intravitreal, periocular or suprachoroidal injection. Systemically administered drugs can reach the eye by the vascular system if they can pass the blood retina barrier and/or blood aqueous barrier. (modified from Zhang, et al.) [1].

Systemic medication is administered either orally or intravenously with its known limitation that only 1-2% reach the target tissue due to BAB and BRB [3].

Using nanoparticles as carriers for therapeutic drugs is a promising approach that could revolutionize unmet medical needs in terms of targeted drug delivery, not only for ophthalmic purposes. It is therefore not surprising that a wide variety of nanoparticles are being investigated as candidates for medical tasks, of which targeted drug delivery is only one example.

First of all, a nanoparticle is defined solely by its size that ranges from 1 to 100 nm. All other chemical, physical, biological and/or physiological characteristics are variable as long as the size criterion is met. Nanoparticles offer several advantages for the delivery of drugs to ocular (and non-ocular) tissues. They are able to overcome physiological barriers and to release the loaded drug in a timed and sustained manner in their specific target tissue only [1]. To do so, substantially smaller dosages are necessary which minimizes side effects when compared to conventional delivery of the same drug [1].

Method

This review aims at giving an overview of current developments of nano-based drug delivery to the different parts of the eye. Literature was searched and obtained from the PubMed database using the following keywords and useful combinations of those: ‘nanoparticles for drug delivery’, ‘drug delivery to the eye’, ‘nano-based drug delivery to the eye’, nanoparticles ophthalmology’, ‘nanoparticles for ophthalmic drug delivery’, nanoparticles corneal drug delivery’, ‘nanoparticles glaucoma’, ‘nanoparticles retinal drug delivery’, nanoparticles AMD’, ‘types of nanoparticles’, ‘nanoparticle-based gene delivery’, ‘pharmacokinetics of drug delivery to the eye’, ‘drug delivery to the anterior eye’, ‘drug delivery to the posterior eye’, ‘challenges of drug delivery to the eye’, ‘polymeric nanoparticles’, ‘dendrimer nanoparticles’, ‘quantum dots’, ‘nanoemulsion’, ‘nanosuspension’, ‘nanomicelles’, ‘liposome nanoparticles’, ‘solid lipid nanoparticles’, ‘nano-drainage glaucoma’, and ‘nanodiamonds’. We selected literature based on relevance of abstract and/or title. Original as well as review articles have been included. Additionally, backward citation search was performed.

Nanotechnology

A nanoparticle is primarily only defined by its size. All other features are variable. This includes physical, chemical, biological and/or physiological characteristics. A single nanoparticle can consist of a single unit or be a cluster/group of several units as long as the total size remains below 100 nm. There are several ways to categorize nanoparticles based on some of their main characteristics:

a) organic vs. inorganic, b) polymer vs. non-polymer, c) spheric vs. tube vs. rod vs. star-shaped, d) charge of surface. It is almost impossible to mention every single type of nanoparticle that is or has been under investigation for ocular drug delivery. Therefore, we would like to introduce and briefly explain only some basic and fundamental principles of nanoparticle design (Figure 2).

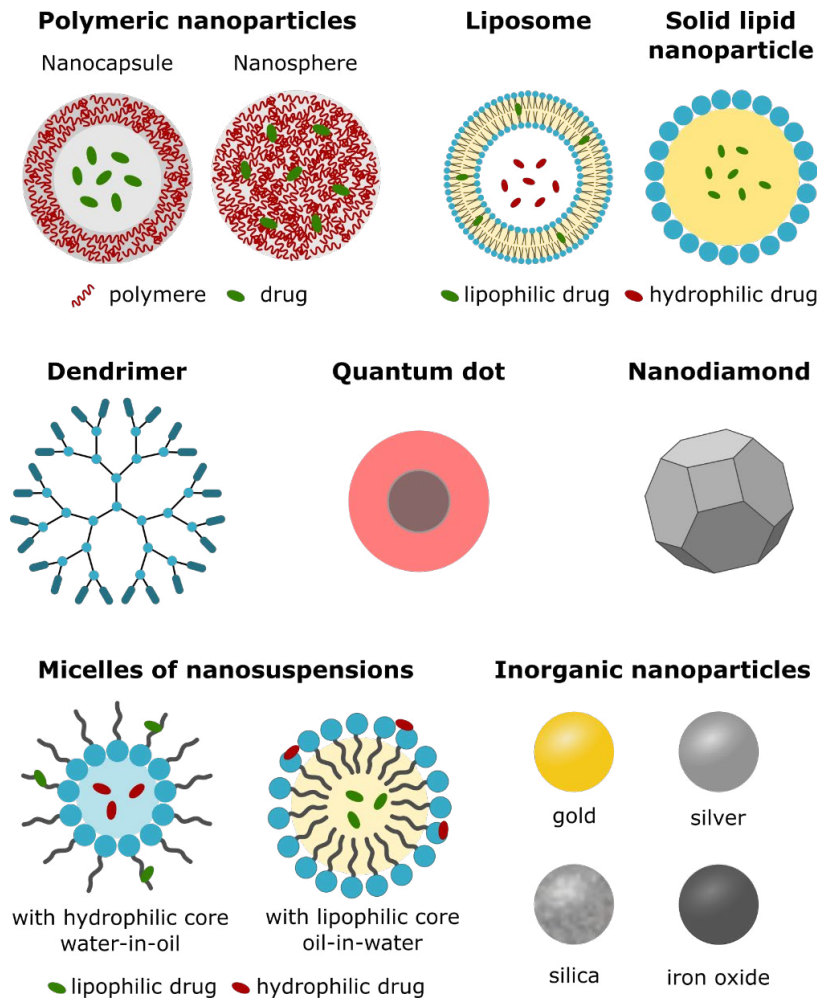


Figure 2: Types of nanoparticles. Basic design of the most commonly used nanoparticles for therapeutic or other medical purposes. First of all, a nanoparticle is defined by its size that has to be below 100nm. All other characteristics are variable. Generally, nanoparticles can be distinguished into organic and inorganic. Further characteristics are shape, surface structure, charge, polymer vs. non-polymer etc. Please note that the above shown sizes are not true to scale.

Polymeric Nanoparticles

Polymeric nanoparticles (PNP) are spherical particles that range within the size of 1 to 1000 nm. PNPs can be designed as nanospheres or nanocapsules. PNPs can be loaded with active compounds either on their surface or trapped within the PNP [4]. PNPs offer the possibility of sustained drug release, protect the loaded drug from degradation and they have shown excellent safety profiles in human use [4,5]. Both natural and synthetic polymers are used. Examples for natural polymers are chitosan, gelatin, sodium alginate, albumin, heparin, dextran and hyaluronan [4,6]. Natural

polymers are biodegradable, biocompatible and have mucoadhesive properties. The most commonly used synthetic polymers that have been approved by the US Food and Drug Administration and the European Medicine Agency are poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolide) (PGLA). Approval was based on their good safety profile, confirmed biocompatibility, low levels of immunogenicity and toxicity, and biodegradation [4].

Liposomes

Liposomes are vesicles formed by a phospholipid double-layer. The hydrophilic inside of the vesicle can carry water-soluble drugs while hydrophobic drugs are incorporated into the lipophilic double-layer [1,2,5]. Liposomes are highly biocompatible and degradable and offer several useful modifications: 1) variability of lipid composition, size and electric charge, 2) facilitated targeting due to easily modifiable surface polymers, and 3) almost no antigenicity and no toxicity [2,5]. For example, positively charged liposomes are superior compared to neutral or negatively charged liposomes, as they bind better to the negatively charged corneal epithelium mucinous membrane [7,8]. Similarly, coating of liposomes with bioadhesive polymers, e.g. chitosan, enhances the corneal residence as well [9].

Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are synthesized from various lipids such as lipid acid, mono-, di- or triglycerides, glyceride mixtures or waxes. In contrast to liposomes, SLNs have a solid lipid core and a hydrophilic surface. Their size usually ranges between 50-1000 nm and they remain in the solid state at body temperature [10]. When prepared from physiological lipids, SLNs do not show any biotoxicity [11]. Above that, SLNs are able to control drug release, offer drug targeting, long-term stability, good drug loading, easy large scale production, and they can be sterilized via autoclaving [11].

Nanosuspension

Nanosuspensions contain pure drug nanoparticles in nano-scale range. A nanosuspension is generally stabilized by surfactants or polymers. Nanosuspensions provide increased contact area and residence time between drug and tissue (e. g. cornea) and they are especially suited to increase the bioavailability of poorly soluble drugs [1].

Nanoemulsion

A nanoemulsion is a dispersion of two different liquid types consisting of micelles that are 100 nm in diameter or less. Some emulsions need surfactants and/or other additives to induce thermostability and to enhance membrane permeability [1,5,12]. Nanoemulsions can either be produced through oil-in-water or water-in-oil emulsification (Figure 2) [12].

Nanomicelles

Nanomicelles are spontaneously formed nanostructures with amphiphilic properties: the lipophilic core portion of the nanomicelle encapsulates the hydrophobic drug, and the hydrophilic portion forms the outer surface. This formation increases drug solubility [1].

Hydrogels

Hydrogels are three-dimensional networks of crosslinked polymers that are able to absorb large amounts of water. By adapting the properties of the crosslinked polymer network, the diffusion

and permeability of hydrogels can be varied. As hydrogels can be formed at ambient temperatures, making them ideal candidates to carry fragile entities, such as antibodies, peptides, cells, proteins or oligonucleotides [2]. Hydrogels can be used periodically or intravitreally.

Dendrimers

Dendrimers are spherical nanoparticles with a core molecule to which branched units are added in a regular and repeated manner. With each additional branched unit, the diameter increases linearly while the number of terminal groups and the molecular weight increase exponentially [13]. The unique structure of dendrimers offers some useful properties that other nano structures do not share to the same extent. Modification of the terminal groups allows higher prediction and higher control of the bio-distribution and drugs can be loaded via different kinds of connections as direct conjugation, ionic interactions, or even trapped in the core of the dendrimer [13]. The most commonly investigated dendrimer is synthesized out of the polymer polyamidoamine (PAMAM), but other materials such as phosphorous, carbosilane, and peptides are under investigation as well [13].

Quantum Dots

Quantum Dots (QDs) are semiconductor nanoparticles that emit light of a single wavelength when their electrons are excited by light of a specific wavelength. The color of the emitted light depends on the size of the QD. Larger QDs emit shorter wavelengths and smaller QDs emit longer wavelengths [14]. The most commonly studied QDs are those with zinc sulfide core (CdSe/ZnS-QDs) protected by a zinc sulfide shell. Their aforementioned physical ability to emit light upon excitation and their ability to cross biological barriers have made QDs promising candidates for in-vivo imaging. However, since their surface is also modifiable, i.e. conjugation with functional groups (genes, stem cells, receptor agonists, drugs), QDs are as well under investigation as nanocarriers for targeted delivery [14].

Inorganic Particles

Inorganic nanoparticles that are used for medical purposes include gold, silver, cerium dioxide, silica and inorganic salts. Gold, silver and cerium already have physiological properties on their own, such as antimicrobial or antioxidant effects. In addition, they are also used as nano-carriers [6]. Silica nanoparticles and inorganic salts qualify as nano-carriers due to their large surface area, biocompatibility and biodegradability. Commonly used inorganic salts are calcium carbonate and calcium phosphate [6].

Nanodiamonds

Nanodiamonds are carbon-based nanoparticles with a truncated octahedral structure. They are non-toxic and their large surface area is highly tailorable [15].

In summary, nanoparticle-based delivery of therapeutic drugs has several advantages. Firstly, the bioavailability of the carried drug

is increased in the target tissue as nanoparticles can overcome physiological barriers of the body. Furthermore, by modification of the nano-carrier, delivery to only the target tissue is achieved, making it possible to reduce drug dosage and side effects. Secondly, solubility of the drug is increased, thereby reducing side effects of conventional solvents that become obsolete. Thirdly, nanoparticle-based drug delivery increases the elimination half-life of the drug, thereby increasing blood concentration time and efficiency of the drug. As a consequence, frequency of use as well as toxic and side effects are reduced [1].

Nanoparticle-Based Drug Delivery to the Anterior Segment of the Eye

Challenges of Topical Drug Delivery to the Anterior Segment of the Eye

There are various diseases and/or conditions of the anterior eye that require treatment with therapeutic drugs including dry eye, inflammatory diseases, infectious diseases, glaucoma, hereditary

and degenerative diseases, injury, trauma, ocular manifestations of systemic diseases, cataract, congenital and developmental abnormalities as well as tumors [10]. In general, there are four possible routes of drug delivery to the anterior segment of the eye: topical, intracameral, subconjunctival, or systemic [10,16]. Depending on the route, one or more ocular barrier must be overcome to reach the site of action. By far the most commonly chosen route is the topical application of eye drops and/or ointments. However, this route of drug administration has its limitations, namely limited penetration to the tissue of interest, need for repeated dosing to reach effective therapeutic levels, and rapid washout by the tear-film and lacrimal drainage. As a consequence, bioavailability is limited to less than 5% of the initially applied dose via this route of administration [2,6,16]. Figure 3 shows the elimination pathway of topically administered drugs.

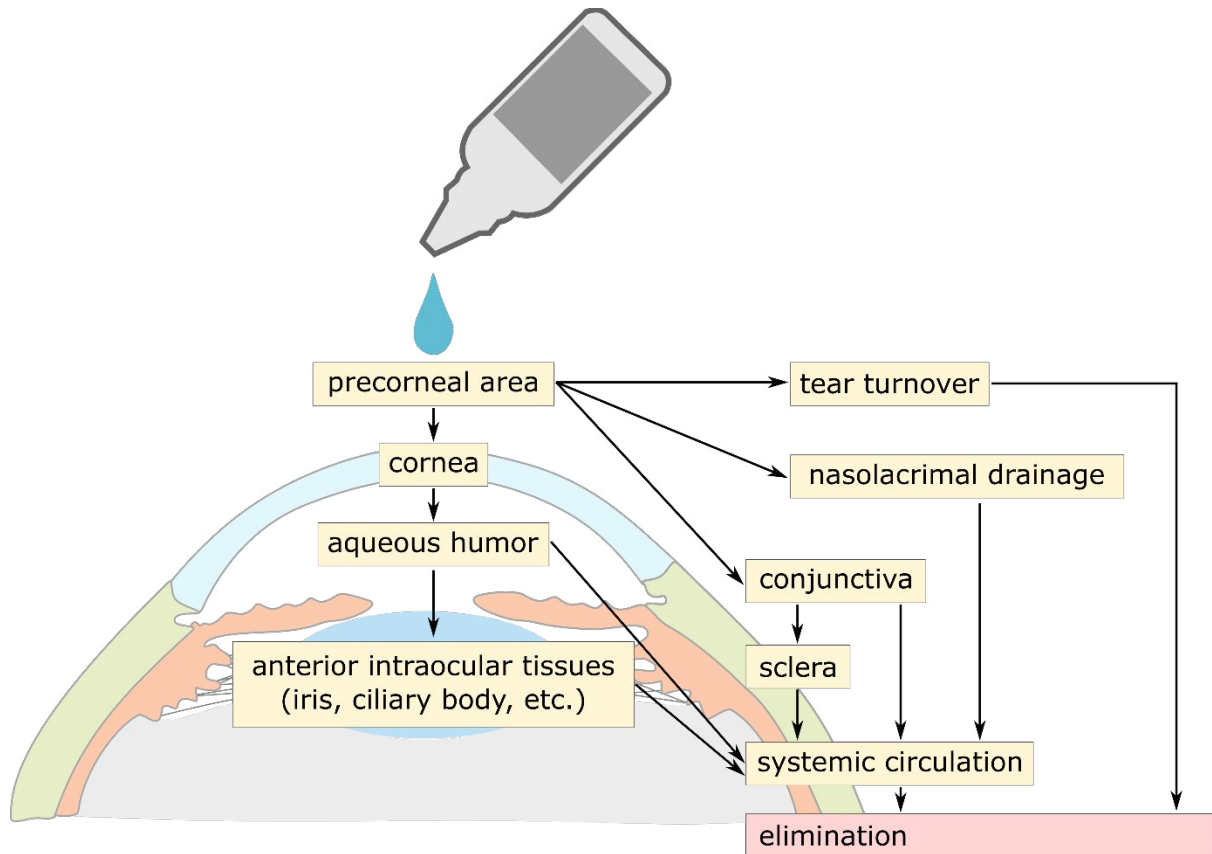


Figure 3: Elimination pathway of topically instilled drugs. Eye drops or eye ointments are instilled to the precorneal area. The drug is then confronted with tear turnover, and nasolacrimal drainage, two mechanisms that reduce the amount of drug that can reach the target tissue. There are two ways for the drug to enter the eye: 1) precorneal area - cornea (penetration) – aqueous humor – anterior intraocular tissues, and 2) precorneal area – conjunctiva – sclera. Finally, the drug is eliminated via entry in the systemic circulation. (modified from Janagam, et al.) [10].

There are two routes by which drugs can reach internal anterior structures of the eye after topical administration. The first is via diffusion through tear-film and cornea into the anterior chamber, the second is penetration through the conjunctiva and sclera [6,10,16]. Although the conjunctiva is more permeable than the cornea and its surface area is about 17 times larger, the main absorption route

is through tear-film and cornea [6]. The reason for this is the high loss of drug into the systemic circulation via penetration through conjunctiva and sclera.

Figure 4 shows the layers of tear-film and cornea that have to be penetrated by drugs.

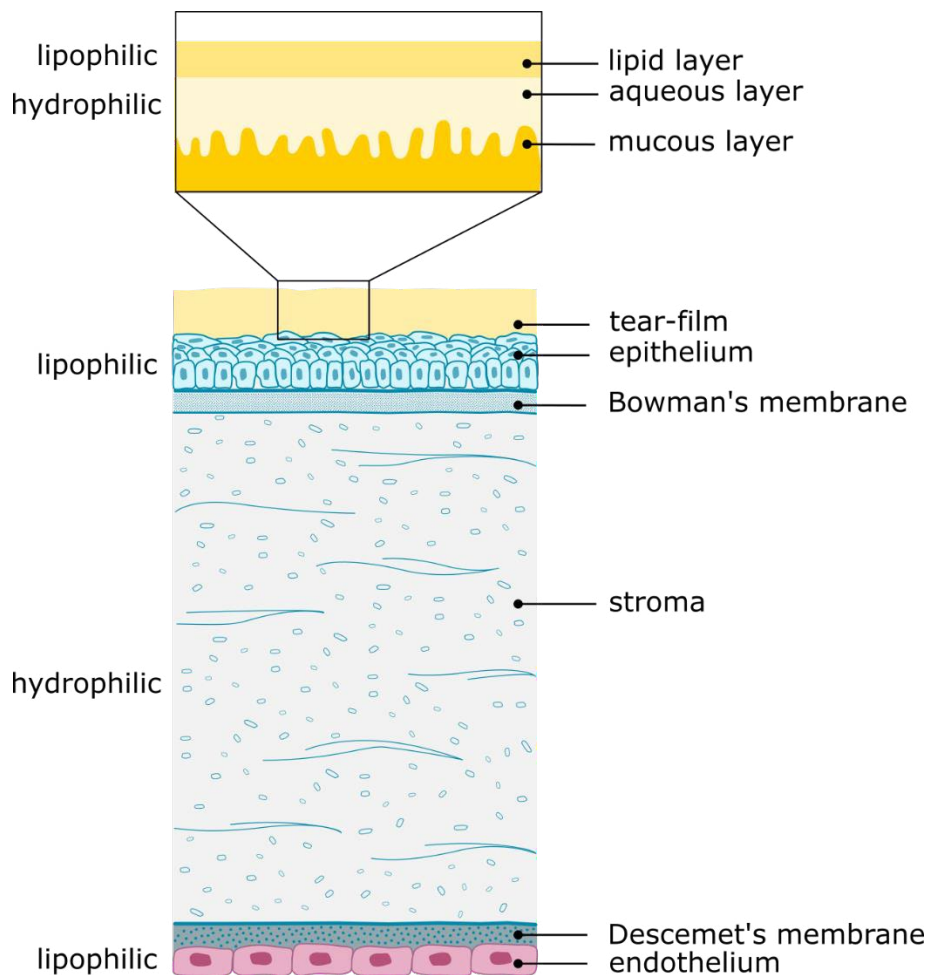


Figure 4: Layers of tear-film (top) and cornea (bottom) that have to be penetrated by topically instilled drugs. The tear film forms the first barrier. It consists of an outer, lipophilic layer, followed by a hydrophilic middle layer, that finally merges into the mucous layer. The latter lies directly on the corneal epithelium, a multilayered lipophilic cell layer. Bowman's membrane forms an interface between corneal epithelium and corneal stroma. The hydrophobic stroma forms the thickest layer of the cornea, which is bounded toward the interior of the eye by Descemet's membrane and finally by the lipophilic corneal endothelium. (modified from Vaneev, et al.) [6].

Nanoparticles have the ability to overcome the above-described barriers in the eye based on their size and design. In addition, they can prolong the contact time between drug and target tissue, as well as they can provide protection against rapid degradation of the drug. In addition, if designed accordingly, they allow continuous drug release over longer periods of time. The latter is especially important when patient compliance is poor.

Conjunctiva

The conjunctiva is anatomically the most accessible structure of the anterior segment with regard to drug application. However, the

above-described difficulties in terms of reduced bioavailability of conventional topical drugs also apply here.

Liu, et al. recently summarized nanotechnology-based approaches for the treatment of the group of allergic conjunctival diseases [12]. They report that immunomodulators, NSAIDs and corticosteroids have been incorporated into nano-based carriers [8,17-32]. The predominantly used types of nanoparticles were liposomes, solid lipid nanoparticles, polymeric nanoparticles, nanomicelles and nanoemulsions. In summary, the nano-formulations showed high encapsulation efficiency, provided controlled and sustained release

of the encapsulated drug, had better permeability characteristics, achieved high therapeutic drug levels, showed enhanced muco-adhesion and increased corneal retention time, and had favorable safety profiles when compared with conventional eye drops of the investigated drug [12].

Cornea

Another interesting research field for nanoparticle use is the treatment of diseases of the corneal endothelium via transplantation of whole and/or parts of the cornea. Three different approaches are followed [33]. The first is the treatment of donor cornea (either for lamellar keratoplasty or for DSAEK or DMEK) before it is transplanted into the recipient's eye. The goal is to improve the quality of endothelial cells by modification in the corneal bank. For this purpose, nanoparticles are ideal carrier candidates, to transport health promoting molecules or genes into the endothelial cells. Another approach is the injection of cultured endothelial cells into the anterior chamber that have been infected with magnetic nanoparticles. To avoid the loss of injected cells by the aqueous humor cycle and to target the cells to the posterior side of the cornea a magnetic contact lens is used after injection to direct the cells to their desired location [33]. The third approach aims at preventing or at least delaying transplantation. For this purpose, the corneal endothelium of the patient is treated with therapeutically active nanoparticles that are directed to the endothelial cells via the aforementioned magnetic technique [33].

Of course, not only diseases of the corneal endothelium are of interest for nanotechnology-based therapy. Several formulations are under investigation to treat infectious or non-infectious keratitis. A nano-chitosan formulation, for example, showed anti-amoebic activity in an in-vitro study against *Acanthamoeba* spp. [34]. The authors postulate that nano-chitosan is an excellent candidate for future in-vivo treatment approaches of *Acanthamoeba* keratitis. The group of Huang et al. developed a hybrid-hydrogel-based contact lens with chitosan, silver particles and graphene oxide. The latter can be loaded with voriconazole. The contact lenses significantly enhanced the therapeutic effects in vitro and in an animal model of fungal keratitis [35]. The broad-spectrum antifungal ketoconazole has been incorporated into a lipid-polyethylene glycol formulation, that showed increased bioavailability of ketoconazole in aqueous and vitreous humor, plus a good safety profile in a rabbit model [36].

Uzunalli, et al. designed a bioactive peptide nanofiber to treat defects of the corneal stroma caused by trauma or disease. The laminin and fibronectin containing nanofibers increased keratocyte migration and supported stroma regeneration in vitro and in vivo (rabbit cornea) [37]. Another, very promising system was developed by Baran-Rachwalska, et al. [38]. The group has designed a unique silicon-lipid nanoparticle that allows siRNA to be introduced into the eye for siRNA-based gene silencing. The nanoparticle penetrated all corneal layers and it resulted in significant reduction of the targeted protein expression [38]. The system is very

versatile as it can be loaded with every desired siRNA.

Another major field that nano-based drug delivery is dedicated to is dry eye disease (DED). DED is a common multifactorial disease of global relevance [39]. DED leads to eye discomfort, ocular surface damage and visual disturbance with negative impacts on the quality of life of the patients [39,40]. Nanocarriers have the potential to revolutionize treatment of DED as they can provide site specific and sustained delivery of therapeutic agents [40]. Not surprisingly, countless nano-based formulations have been or are currently being investigated. Most formulations aim to improve ocular surface moisturization, but some anti-inflammatory or immunomodulatory formulations have also been developed [1,39,40]. Examples for marketed nano-based eye-drops are the propylene glycol-based nanoemulsions by Alcon (SYSTANE® portfolio) or liposomal eye drops by Bausch&Lomb (Artelac Rebalance®).

Glaucoma

Glaucoma is primarily treated via topically applied intraocular pressure (IOP)-lowering eye drops. Since patients usually have to administer the drops several times a day for the rest of their lives, compliance is often poor, especially when ocular surface side effects occur.

Several classes of IOP-lowering drugs are available, including β -blockers, prostaglandin analogs, carbonic anhydrase inhibitors, α -2 agonists and cholinergic agents [7]. The choice of the appropriate nano-carrier depends on the characteristics of the drug regarding hydrophobicity, size and stability and on the target tissue [7]. So far, anti-glaucomatous drugs have been incorporated into several types of nano-carrier such as liposomes, niosomes, PNPs, dendrimers, nanosuspensions, nanocrystals, nanodiamonds and cyclodextrin complexes [7]. In summary, all nanotechnology-based formulations showed larger and/or prolonged IOP reduction than conventional formulations [7,41]. Most of the experiments were, however, performed in vitro or in animal models, either in vivo or ex vivo. Evaluations of the safety and efficacy in human use is pending for most of them. In 2014, Wong, et al. assessed the safety and efficacy of a subconjunctival injection of a nanoliposome formulation of latanoprost in a small pilot study with six human subjects [42]. The injection was well tolerated by all subjects and the mean baseline IOP of 27.55 ± 3.25 mmHg was lowered by 37-63% within 1h after injection. A significant IOP reduction of $\geq 20\%$ was confirmed for 3 months after the injection. To the best of our knowledge, there have been no further reports on the use of these latanoprost liposomes by Wong et al. since 2014.

In addition to their direct use as drug carriers, nanoparticles are also investigated in combination with larger devices to treat glaucoma. For example, contact lenses are loaded with nanoparticle-based formulations to provide sustained release of antiglaucomatous drugs [7]. Similarly, ocular inserts that are placed into the conjunctival sac can provide prolonged release of drugs [43-45]. An alternative are implantable nano-drainage systems, that pro-

vide a bypass route for aqueous humor outflow [46,47].

The underlying cause of the glaucoma-induced vision loss is apoptosis of retinal ganglion cells (RGCs). An alternative use for nanoparticle technology is transporting a neuroprotective substance to the RGCs to inhibit cell death. Sánchez-López et al. developed a topical formulation of memantine-loaded PLGA-PEG nanoparticles. Memantine is an approved neuroprotective NMDA-antagonist. The memantine nanoparticles showed a significant protective effect on the RGCs in a rodent glaucoma model. It was also safe and well tolerated [48].

Lens and Posterior Capsule

The lens is the most internal structure of the anterior eye. In the following, two possible applications for nanotechnology regarding the lens are presented. The group of Huang et al. coated an intraocular lens (IOL) with 5-fluorouracil chitosan nanoparticles (5-Fu-CSNP) to prevent posterior capsular opacification (PCO) after cataract surgery. They report superior results *in vitro* and in an animal model when compared with a 5-Fu solution without chitosan [49]. Another modification of IOLs has been performed by Lin, et al. [50]. They coated the rim of commercially available IOLs with silica coated gold nanorods that block the formation of PCO. In rabbit models, PCO was reduced by 60-70% when compared to the control group with 100% PCO occurrence [50].

The formation of cataract is accelerated in diabetic patients caused by hyperglycemia-induced oxidative stress [1]. Intraperitoneal treatment of diabetic rats with a mesoporous silica nanoparticle loaded with Cerium (III) chloride efficiently ameliorated the progression of diabetic cataract. The same result could be reached by subconjunctival injection of autoregenerative redox nanoparticles (CeO₂ coated with PEG-PLGA) in the same diabetic rat model [51]. Future experiments should try to adapt these treatments into a non-invasive approach.

Nanoparticle-Based Drug Delivery to the Posterior Segment of the Eye

Diseases of the posterior segment are a major cause of blindness worldwide each year. Especially diabetic retinopathy (DR) and age-related macular degeneration (AMD) have to be mentioned in this context. In addition, there are many other diseases of the retina and the choroid that require treatment. Current treatment options for diseases of the posterior segment include photocoagulation, cryocoagulation, intravitreal injections of therapeutic drugs and vitrectomy. Intravitreal injections have become the gold-standard for the treatment of AMD, for example. However, frequent injections are necessary, on the one hand because of the relatively fast clearance of the drug from the vitreous space, and, on the other hand, because of the progression, persistence or recurrence of the underlying disease.

The various nanoparticle systems and their variable and adjustable characteristics offer the possibility to design NPs for intra-

vitreal use with targeted, controlled and sustained release of e. g. anti-VEGF inhibitors or corticosteroids. Additionally, researchers are also investigating topical formulations for drug delivery to the retina or other posterior structures of the eye, because frequent intravitreal injections increase the risk of endophthalmitis, retinal detachment, vitreous hemorrhage or cataract formation [52,53].

Regardless of whether drugs or drug delivery systems for the posterior segment of the eye are administered topically or intravitreally, various anatomical and physiological barriers have to be overcome [54,55]. These barriers represent the first major challenge for the design of efficacious nanoparticles. Once the site of action is reached, a long therapeutic effect without eliciting local side effects is desired [52,54]. In a review by Huang and Chau, four major characteristics of nanoparticles are discussed that influence the efficiency of their intraocular distribution and elimination [52]. These four characteristics are size, surface charge, stability and ligands. Additionally, the authors proposed a simplified pharmacokinetic model of the intraocular distribution, retinal penetration and elimination of intravitreally injected nanoparticles. The authors conclude, that optimal nanocarriers for targeted and sustained retinal delivery are a product of the combined effects of their size, surface charge, stability, ligand design as well as of the changes that are expected to occur *in vivo* [52].

Topically applied nano-formulations targeting the posterior eye, have to overcome the barriers of the anterior eye, which we already discussed above, in addition to the intraocular structures as vitreous and the vitreoretinal interface [53,54]. Recently, Löscher, et al. specifically reviewed topical drug delivery to the posterior segment [53]. The authors identified four major types of drug delivery systems (DDS) that are especially suited to accomplish posterior drug delivery via topical administration. The four DDS are amino acid/peptide-based, lipid-based, DNA-based and carbohydrate-based. Except of the amino-acid/peptide-based DDS all systems represent nanotechnology-based approaches [53]. It is further summarized that a wide variety of drugs has been incorporated into these DDS and that several different diseases are addressed including AMD, glaucoma, retinal ischemia, diabetic retinopathy, and central macular edema.

Gene or siRNA Delivery to the Eye via Nanotechnology

The permanent introduction of genes into cells of the retina or other specific tissues of the eye is a promising technology to treat inherited diseases. Based on their large variety and variability, nanoparticles are ideal candidates to perform this task. The success of nanoparticle-based gene delivery depends on three key steps: the internalization of the loaded nanoparticles into the target cells, the escape from endosomal vesicles, and the transfer of the plasmid DNA into the nucleus [56]. So far, several types of nanoparticles have been used for gene delivery: metal, lipid and polymer nanoparticles [56-61].

In comparison to the alternative gene delivery method mediated

by adeno-associated virus (AAV)-vectors, nanoparticles can carry plasmids up to the size of 20 kbp, while AAV-vectors are limited to 5 kbp [56]. On the contrary, transfection of cells is currently more efficacious via AAV-vectors than via nanoparticles, but researchers are confident that the easy and diverse modification options of nanoparticles can remedy this deficit in the near future. Instead of carrying plasmid DNA, nanoparticles can likewise carry siRNA to silence specific genes by RNA interference [62]. This method is well suited for the treatment of acute diseases.

Challenges and Disadvantages of Nanoparticles

Although nanoparticles seem to be promising candidates for the safe, targeted and sustained delivery to all parts of the eye, there are also some challenges that influence the development of potent formulations. The challenges vary between different nanoparticle types. With liposome-based formulations, for example, several problems such as leakage of the enclosed drugs, poor long-term stability, high cost of large scale production, difficulties with sterilization and sometimes low drug loading can occur [1]. Nano-suspensions and nanoemulsions can cause irritations or even toxic side effects when surfactants are needed [1]. Polymeric and lipid nanoparticles have only insufficient capability to carry watersoluble drugs and for effective topical use, introduction of increased mucoadhesion is necessary [1].

On the one hand, nanoparticles have excellent characteristics that could overcome unmet needs of conventional drug delivery. However, nanoparticles themselves, depending on some of their properties, may induce toxic effects to the body. Nanotoxicity studies investigate this potential risk. Possible negative effects of nanoparticles are cell toxicity, immunotoxicity and genotoxicity [63]. Iron-based nanoparticles, for example, can induce oxidative stress which leads to cell damage via several ways [64]. Therefore, toxicological assessments should always accompany the development of nanoformulations that are intended for human use.

Conclusion

As a result of their small size and modifiable surface nanoparticles are able to overcome ocular barriers that would otherwise be impassable. Furthermore, their large surface to size ratio is favorable for carrying and releasing drugs in a controlled fashion at a desired target location. Due to these properties, nanoparticles have the potential to overcome limitations of conventional therapeutic systems, such as low bioavailability of the drug, need for frequent application, and reduced permeation of ocular structures [1]. Many in vitro and in vivo studies in animal models have confirmed this potential and some formulations are already marketed for human use.

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