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NANOTECHNOLOGY IN THE TREATMENT AND DETECTION OF INTRAOCULAR CANCERS

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Abstract

Tremendous progress in nanotechnology has lead to the development of nanometer-sized objects as medical implants or devices. Many of these nanodevices have recently been tested in many cancer diagnostic and therapeutic applications, such as leukemia, melanoma, breast tumor, prostate tumor, and brain cancer. Despite the increasing importance of nanotechnology in cancer, the potential of these nanodevices in diagnosing and treating intraocular cancers has not been systematically evaluated. This review summarizes the significant advancements and potential areas for development in the field of nanotechnology-based intraocular drug delivery and imaging.

Keywords

Intraocular cancer; uveal melanoma; retinoblastoma; nanoparticles; liposomes; quantum dots; intravitreal injection; drug delivery; imaging

1. Intraocular Cancers – Overview and detection

Though less common, the risk of complications and metastatic potential of intraocular cancers presents a very dangerous condition, warranting the same vigilant management as other cancers. Due to their proximity to critical ocular structures, early diagnosis and treatment of intraocular cancer are essential to preserve vision. There are two common forms of intraocular tumors which can be characterized based on the typical age of occurrence: ocular melanoma in adults and retinoblastoma in children. Ocular melanoma is the most common malignancy originating in the eye in older patients with a median onset age of 55.[1,2] Retinoblastoma is a very common form of ocular malignancy occurring in children.[1]

Uveal melanoma is the most common type of ocular melanoma and typically presents as a small tumor near critical structures in the eye.[1,3] The potential causes and risk factors of uveal melanoma remain undetermined,[6] though incidence is slightly higher in men, with rates 150 times higher in Caucasians compared to those with darker skin. This is consistent with the statistically higher incidence seen in patients with light skin, blue eyes, and blonde hair.[1] Compared with other intraocular tumors, uveal melanoma has the highest rate of metastasis, with a 40% metastasis rate (median survival 2–7 months) and approximately

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50% of mortal cases due to metastasis, most commonly to the liver.[2,5] Approximately 30% of patients with successfully treated primary tumors will develop metastasis.[5]

The most concerning issue with this condition are problems with detection and treatment.[5] As such, the rate of metastasis and mortality has remained unchanged over the years. Typically, uveal melanoma is diagnosed by binocular indirect ophthalmicroscopy.[6] Indocyanine green angiography is also used to visualize the tumor and tumor margins.[6]

The most common treatment options include enucleation, local resection, brachytherapy, of which brachytherapy would represent the most common.[6] These approaches are plagued by high failure rates and complications with large tumors or those near the optic nerve,[4] with other complications including iris neovascularization and neovascular glaucoma.[7] External beam radiotherapy has success rates similar to enucleation, providing local control and organ preservation along with unmatched cosmetic results and visual preservation.[3] Chemotherapy using drug or drug combinations has also been employed (Table I). Some common active chemotherapeutic drugs used to treat advanced melanoma include dacarbazine (DTIC) and cisplatin.[8,9] Single agent response rates with chemotherapy are below 10%.[11] Thus, the general trend of chemotherapy is to include multiple drugs/agents simultaneously. For that, the major challenge is how different drugs/agents would be constantly and locally delivered to the tumor site for a prolonged period of time.

Despite the wide range of available treatments, the problem of metastasis remains, due to our inability to detect the development the tumor at early non-symptomatic period.[5] This is complicated by the fact that a recent UK study suggests approximately 45% of patients were asymptomatic at the time of tumor diagnosis.[6] Several imaging modalities are under investigation for use in the detection and analysis of treatments in uveal melanoma. Functional MRI has been used to detect uptake of magnetic contrast agents and determine perfusion and blood volume in uveal melanoma.[12] Positron emission tomography has been investigated to detect liver metastasis in patients with uveal melanoma.[13] However, none of these methods can be used to detect uveal melanoma in its early stages.

Retinoblastoma, often a hereditary condition, occurs in children under 5 years of age and is caused by inactivation of the RB gene. The incidence of this form of intraocular cancer is highest in the developing countries.[14] Inactivation of this gene takes off constraints on cell-cycle control leading to unregulated cell proliferation. The cancer presents itself as either an abnormal white discoloration in one or both pupils or as an ocular misalignment due to loss of central vision in the eyes. In advanced cases ocular swelling is seen due to extraocular invasion of the tumor. Large retinal tumors often lead to retinal detachment. Retinoblastoma can spread to the subarachnoid space and from there to the brain and spinal cord. It can also invade the choroid vasculature and spread to the bone and bone marrow.[15]

Diagnosis of retinoblastoma is usually by examination and imaging of the eye by an ophthalmologist. Detection is by funduscopy, which typically shows a large white to creamy colored tumor with lesions around the retinal and vitreous space.[16] The intraocular tumor is identified and analyzed by ultrasonography since CT scan is not recommended for small children.[17] Magnetic Resonance Imaging (MRI) of the brain and the orbits is conducted to examine the extraocular extension of the tumor.[18]

Chemotherapy and enucleation are the common treatment methods for children with advanced retinoblastoma. Typical chemotherapeutic drugs include carboplatin, vincristine, cyclophosphamide and doxorubicin.[16,19] Some other treatments have also been used. For example, thermotherapy involving the application of heat in the form of infrared radiation directly on to the tumor or chemothermotherapy with a combination of chemotherapy and

thermotherapy.[16] The common chemotherapeutic drugs used for treating uveal melanoma, [8,9,16] and retinoblastoma [16] have been summarized in Table I.

Despite the various treatment methods available, almost all current treatments fail to completely eradicate cancer or prevent its recurrence.[19] The ineffectiveness of chemotherapy agents may be associated with the inability to deliver large amount of chemotherapy drugs into tumor tissue in vivo.[20] Studies have found that most systemically administered drugs are consumed by other organs/tissues prior to accumulating in cancer tissue. Such deficiency can not be resolved by increasing the amounts of administered drugs, since it is well established that certain chemotherapy agents have inherent systemic side-effects, including bone marrow toxicity.[21] To maintain a therapeutic dosage of chemotherapeutic drug at the ocular tumor site, it is imperative that anti-cancer drugs be targeted, delivered and released at the cancer site.

To achieve localized release of anti-tumor agents, many different methods have been tested including intra-tumor injection, intra-tumor implantation, and targeted delivery.[22,23] Such approaches may not be suitable to combat ocular tumor, since invasive surgical procedures are difficult to carry out in eye and surgical trauma associated with the operation may lead to vision impairment. To avoid such complications, increasing research interests have been placed on the development of nanodevices which can target the tumor for both tumor drug delivery and imaging. Such efforts are summarized as the following.

2. Nanodevices for ocular tumor

Although significant progress has been made in the application of nanotechnology-based cancer diagnostics and therapy for the rest of the body, a very limited number of studies have been done to develop nanodevices for ocular tumor treatment. Some studies, however, have been varied out on the use of nanoparticles for tissue targeted and slow drug release in various structures of the ocular tissue. The outcomes of those works are summarized below.

2.1. Delivery routes for ocular drug delivery

Numerous works have focused on evaluating the efficacy and limitations of different implantation methods on the extent of drug diffusion and retention in ocular tissues.[24–29] Some of the ocular drug administration routes are topical treatment, systemic, intravitreal, subconjunctiva, suprachoroidal, juxtascleral, and subtenon injection (Figure 1). Each ocular drug delivery route has unique advantages and disadvantages that are related to where the nanodevices are positioned in the ocular tissues. Systemic administration via intravenous injection is the most popular method to deliver drugs to many parts of the body. However, studies have shown that very small portions of systemically administered drugs/nanodevices are found to accumulate in the ocular tissue.[30] The majority (>90%) of ocular drug delivery relies on topical administration via eye drops. The success of such treatment depends on the efficacy of spontaneous diffused drug or drug-eluting carriers through the cornea.[28,31–34] Although topical administration has shown some success to treat anterior chamber eye diseases (diseases associated with cornea and iris), such treatment is often found to be ineffective in treating posterior eye diseases, including retina diseases and intraocular tumors.[35] It is generally believed that this is caused by the inability of drugs to diffuse through the cornea and lens barriers.[35]

Periocular drug delivery through a subconjunctival, suprachoroidal, juxtascleral or subtenon routes offers the advantage of noninvasive approach. However, such treatments often failed to deliver therapeutic dosage of drugs to intraocular tissues for a prolonged period of time. [35–38] Therefore, using biocompatible or cell-specific coatings/receptors intensive research efforts have been placed on periocular drug delivery to enhance the intraocular diffusion of

various devices.[33,39–45] Finally, intravitreal injection of nanodevices is still the most effective method currently available to deliver sufficient amounts of drugs into posterior ocular tissues, including ocular tumor tissues.[35,39,46] However, intravitreal injection may lead to damaging side-effects, such as retinal detachment and endophthalmitis. To reduce such complications, intensive research efforts are placed to produce nanodevices to release drugs for prolonged periods of time which indirectly reduce the requirement for repeated treatments. [43,46] Some of these design strategies that could be adopted for intraocular delivery of nanodevices are summarized in Table II.

2.2 Nanodevices for ocular drug delivery

The design of ocular drug-delivery systems is based on many therapeutic criteria, including carrier tissue compatibility, tissue targeting, drug therapeutic dosage, stability and release rate.[39] Many strategies have been developed to meet such design criteria. These strategies include the modification of drug delivery carrier chemical compositions, physical morphology, degradation rates and tissue affinity. Specifically, carrier chemical composition (material chemical and biological properties) affects drug release and tissue compatibility. The majority of drug release nanodevices are made of polymeric (PLLA, PLGA, polyacrylic acid, or polyamidoamine) or biological materials (oligosaccharides, albumin, or chitosan). Most of these nanodevices are in nanoparticle form with different sizes ranging from 10 nm–1000 nm.[35,39] Nanodevice degradation rates are often affected by material molecular weights and overall tissue responses. Generally speaking, high molecular weights slow down material degradation and strong tissue responses expedite material breakdown.[53] Tissue affinity is determined by both particle size and particle: cell interactions. Increasing numbers of studies have found that tissue has high affinity to particles between 20 nm– 200 nm.[37,38] The specific mechanism(s) governing such size-dependent cellular responses has yet to be determined. It should also be noted that incorporation of cell specific antigen to nanodevices enhances nanodevices' tissue affinity and drug targeting ability.

The recent findings on ocular drug delivery are summarized in the following paragraph. Liposomes containing cholesterol were used for intravitreal delivery of plasmid DNA.[54] Nanoparticles made from chitosan have been used for topical drug administration and found to possess good ocular biocompatibility.[48,55,56] Polymeric PLA and PLGA nanoparticles have been used both topically and intravitreally. These FDA approved polymers have very good biocompatibility and have also shown impressive drug delivery capabilities in both the anterior and posterior chamber. [41,42,51] Intravitreally injected albumin nanoparticles have also been shown to accumulate in the vitreous and ciliary body. [57] Studies have shown that most of these nanoparticles are well tolerated by the body with minimal foreign body reaction and have prolonged residence time.[58] It should be noted that dendrimers,[52,59] and cyclodextrins,[60,61] have been used in different forms of nano-devices. In particular, dendrimers are a relatively new in the field of ocular drug delivery and hence more work needs to be done. Currently, they have been used for anterior chamber drug-delivery applications, although there are concerns of blurring of vision.[59] The applications and outcomes of these nanodevices in intra-ocular drug delivery are summarized in table III. The results from these works and their pros and cons suggest that polymeric nanoparticles have a great potential to serve as intraocular cancer chemotherapeutic drug carrier.

2.3 Nanoparticles for ocular imaging

Many nanodevices have recently been developed to improve imaging quality of conventional imaging modalities. Despite this progress limited research has been done in using nanodevices to improve conventional ocular imaging modalities like MRI, ultrasound imaging and Optical Coherence Tomography (OCT). Despite limited research efforts, many of these nanodevices have shown great promise in improving the imaging and diagnosis of

retinal diseases, including intraocular tumors. Quantum dots have been investigated for their ocular imaging capabilities. They have good optical stability and can facilitate multi-modal detection.[64–66] A recent study which demonstrated the diffusion of quantum dots in to the lens has proven that they can be applied in the eye as well.[67] In addition to quantum dots, nanoshells,[68,69] and gold nanoparticles,[70,71] have the potential to serve as good contrast agents for imaging. Magnetic nanoparticles which can provide good contrast for MRI have been successful in an in vitro setting so far.[24] The limited research done in this area has been summarized in Table IV.

3 Challenges faced in using nanodevices for intraocular tumors

One of the major challenges in the use of nanodevices is their availability in the posterior of the eye which in turn is determined by the administration route. Topically applied nanodevices have to overcome the conjunctival and scleral barriers. Hence the amount of drug delivered to the posterior of the eye would be seriously limited.[28] Even if the nanodevices were to be delivered in the posterior of the eye by injection there are problems of internal ocular bleeding and retinal damage, often caused by the injection itself. In addition there is also a high risk of infections. Systemic injections lead to clearance of the nanodevice from the circulation and systemic side effects. A possible solution for this is the use of intravitreal sustained release systems like microspheres and liposomes.[28,33,43] Subconjunctival and subtenon routes have also shown a lot of promise in delivering drugs and nanodevices to the posterior of the eye.[35]

As with any foreign material, the safety and compatibility of the nanodevices is a major concern. The earliest studies involving ocular drug delivery in humans used latex nanoparticles and nanoparticles made from pilocarpine salt and a co-polymer of laurylmethacrylate-acrylic acid. However, neither of them was successful; partly due to its inability to release drugs in a sustained manner and also due to poor biodegradability and high toxicity.[73] A lot of importance has to be laid on developing nanodevices from materials which have good ocular biocompatibility. In this light, the fact that FDA approved polymers like PLLA and PLGA are well tolerated by the body assumes a lot of significance. In fact, recent research has focused on biodegradable polymers and smart hydrogels.[74–76] PLLA and PLGA nanoparticles have been used to deliver high molecular weight drugs and were found to have accumulated in the retina for long time periods.[43,51,52,75] It has been suggested that low molecular weight polymers like PLGA, which degrade rapidly, are suitable candidates for use as micro and nanospheres.[77] Poly(ortho esters) which are bioerodible have very good ocular biocompatibility. Poly (ε-caprolactone) is well tolerated by retinal tissue for at least 4 weeks.[78] These polymers can be used for delivering hydrophobic drugs. For hydrophilic drugs, hydrophilic polymers of natural origin, like chitosan and hyaluronan serve as good carriers. These are non toxic, biocompatible and biodegradable.[79,80] Hydrogels like poly(N-isopropyl acrylamide) (PNIPAM) have been grafted with chitosan to form a thermally responsive ophthalmic drug delivery device.[81] Coating with chitosan has proven to be advantageous as many corneal and conjunctival cells have high affinity for chitosan.[82] Hence coating with naturally occurring proteins can greatly enhance the ocular biocompatibility.

4 Smart drug delivery and imaging nanodevices for intraocular tumor

The array of nanotechnological approaches in the field of cancer imaging and therapeutics for the rest of the body makes it crucial that more efforts be channeled toward applying them in the field of ocular diagnostics and therapeutics as well. Equally important, in addition to the current single-function nanodevices, part of future research efforts should be placed on developing bi-functional nanodevices to diagnose and to treat cancer simultaneously. Such

devices would allow concurrent monitoring of the intraocular tumor response to various localized release chemotherapeutic drug in to the eye.

We have recently launched studies toward the development of bi-functional nanodevices with this goal in mind. First, rather unexpectedly, we found that poly (N-isopropylscarylamide) (PNIPAM) nanoparticles injected systemically, accumulated more preferentially in the uveal tissue than microparticles made of the same materials.[47] Similarly, intravitreous injection of PNIPAM particles resulted in accumulation in the retina as shown in Figure 2. This could provide many useful clinical options as hydrogel nanoparticles have been shown to have good drug loading and release characteristics.[29,83,84] Subsequent studies were carried out to improve the imaging properties of PNIPAM nanoparticles by physically embedding quantum dots in hydrogel nanoparticles.[66] Using a subcutaneous melanoma tumor implantation model, we have found that quantum dots encapsulated PNIPAM nanoparticles have superior intratumoral accumulation ability.[66] These results support the general concept of bi-functional nanodevices with a quantum dot core and hydrogel shell would aid tumor imaging and drug delivery, respectively. These findings could also be explored for intraocular tumor imaging and treatment.

We believe that more efforts should also be placed on engineering intraocular tumor specific nanodevices. Such nanodevices may be produced by placing ligands or antibodies unique to intraocular tumor cell surface markers. In fact, quite a few studies have been done to identify various markers expressed on uveal melanoma tumor cells. For example, cripto-1 is expressed in uveal melanoma cells and this in fact increases as the tumor size increases.[85] The expression of osteopontin is an indicator of the metastatic potential of uveal melanoma.[86] In addition, our studies have determined the expression of gp 100 and Melan A receptors on more than 95% of the uveal melanoma cells tested. It would be interesting to target these antigens and study the ability of the nanoparticles to be taken up.

5 Conclusion

With the progressive development of nanotechnology in cancer therapy, research efforts are needed to develop cell/tissue-specific nanodevices to meet the challenging demands of intraocular chemotherapy and diagnostics. This review summarizes the overall design criteria and our current understanding on general drug delivery and imaging in eyes. It is our belief that combinatory strategies should be developed to meet different design criteria in order to achieve the ultimate goal of producing “smart nanodevices” against the potent lethal intraocular tumors.

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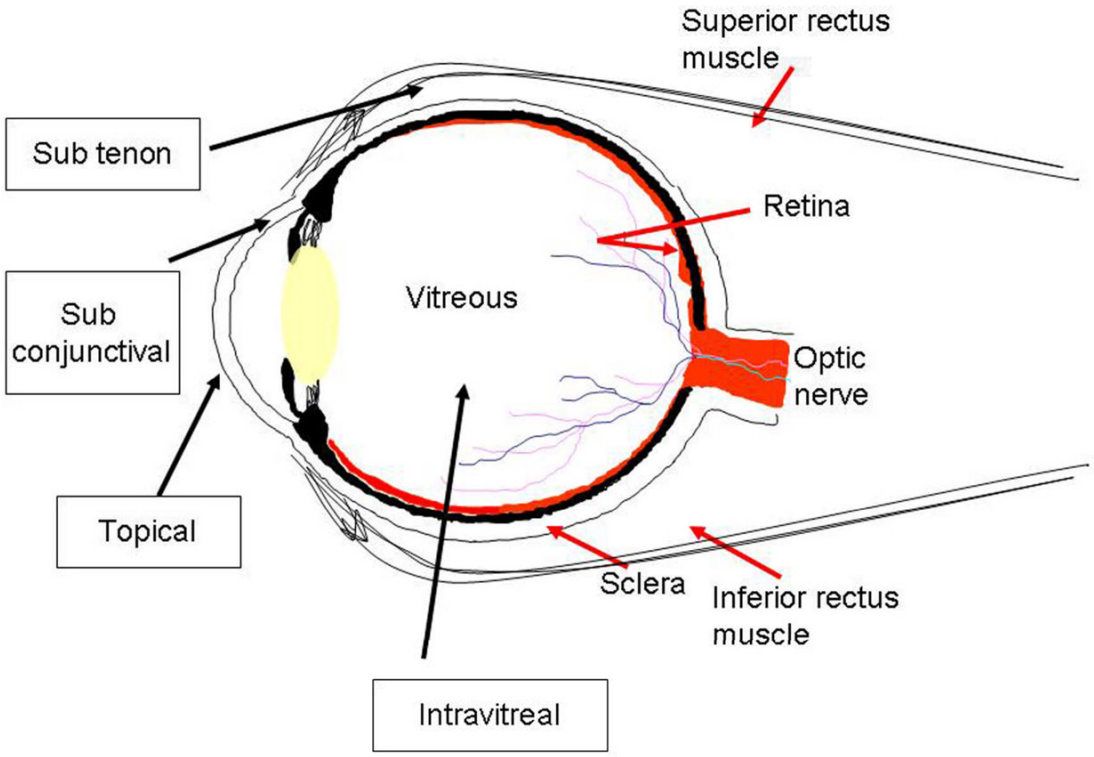

Figure 1.
Schematic showing the eye with some of the routes of intraocular drug/nanodevice administration.[35]

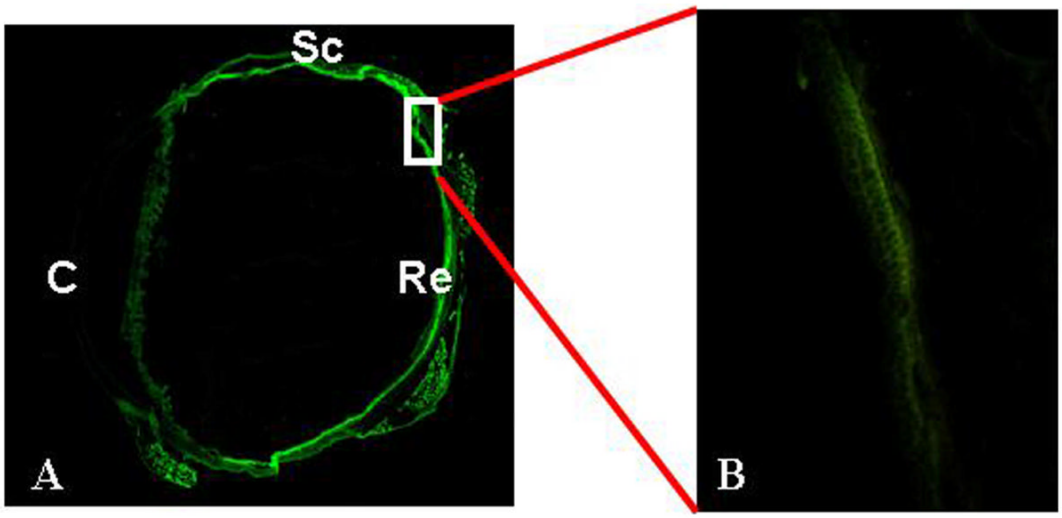

Figure 2.

PNIPAM nanoparticles conjugated with fluorescein dye were injected intravitreous in rabbit eyes; animals were sacrificed. The tissue sections were then imaged to document the distribution of nanoparticles. Most of the particles accumulated in the retina tissue in 24 hours (A). A closer look at the section under a microscope showed that the particles were preferentially accumulated in the retinal layer (B). Specific ocular tissues are labeled as follows: C: Cornea; Sc: Sclera; Re: Retina

Table I

List of chemotherapy drugs commonly used for the intraocular tumors.

Type of intraocular cancer	Chemotherapeutic drugs	References
Intraocular retinoblastoma	Vincristine, etoposide, carboplatin	_16
Uveal Melanoma	Dacarbazine (DTIC) Cisplatin	8
	Dartmouth regimen (Cisplatin + Carmustine + DTIC + Tamoxifen)	10
	Chemoimmunotherapy (α-IFN/IL-2)	10

Table II

Design strategies for ocular cancer therapy based on administration route and material selection

Adminstration route	Drug release venues	Carrier Materials	Advantage	Disadvantage
Systemic	*Injection in to blood stream*	Degradable and hydrogel nanoparticles. Eg: N isopropyl acrylamide (NIPAM) nanoparticles.[47]	Less invasive to ocular tissue	Blood ocular barrier hinders drug delivery; potential systemic drug toxicity.[34]
Topical	*via corneal diffusion*	Nanocapsules, nanoparticles and mucoadhesive polymers Eg: Chitosan nanoparticles.[48]	Easy access to iris and ciliary body. 33,34	Poor drug delivery efficiency and unsuitable for posterior eye diseases.[28]
Sub-conjunctiva	*Released from conjunctiva tissue*	Polymeric nanoparticles.[37] eg:polystyrene nanoparticles various sizes & charge	Prolonged drug release with increased drug delivery to uveal tissue.	Small (<20nm) nanoparticles may be cleared by lymphatic. 37,38
Sub-tenon	*Released from void space between Tenon's capsule and sclera*	No studies on subtenon injection of nanodevices. Mainly used for injection of drugs.[49,50]	Prolonged drug penetration and low clearance from vitreous tissue.[35]	Requires skilled surgeon for implantation and retinal pigment epithelium poses a barrier.[35]
Intravitreal	*Direct injection in to the vitreous*	PLA/PLGA nanoparticles.[43,51,52]	Deliver high molecular weight drugs. Accumulation in the retina for long time periods.[51]	May cause retinal detachment & endophthalmitis

Table III

Effect of material composition and drug delivery routes on the efficacy of nano-device drug delivery in eyes

Nanodevice	Location	Nanodevice Type	Outcome	References
Liposome	*Anterior chamber*	Cationic liposome-drug and peptide delivery	Better drug delivery than topical ointment.	31,32
	Posterior chamber	Sterically stabilized liposome - Oligonucelotide delivery	High delivery efficiency.	54,62
Polymeric nanoparticles	*Anterior chamber*	Chitosan nanoparticles	High conjunctival & corneal penetration than free drug. Good tissue compatibility	48,55,56
		PLA nanoparticles with PEG coating	High drug delivery	41,42
	Posterior chamber	PLA nanoparticles injected intravitreous	Migration toward retina and accumulation in retinal pigment epithelial cells up to 4 months.	42
		PLGA nanoparticles with pigment epithelium derived factor (PEDF)	Possess neuroprotective effects.	51
		Albumin nanoparticles	Accumulate inside the vitreous and ciliary body	57
Dendrimers	*Anterior chamber*	Poly(acrylic) acid & poly(amidoamine)	Enhanced biorecognition with blurring of vision.	59,63
Cyclodextrins	*Anterior chamber*	Cyclic oligosaccharides	Well tolerated with enhanced release of drugs.	60,63
Nanosuspensions	*Anterior chamber*	Eudragit RS 100® and RL 100 ® polymer resins	High corneal adhesion Well tolerated since no toxic chemicals.	58,61,63

Table IV

Potential applications of nanodevices for ocular imaging

Nanodevice	Pros and Cons	Current applications
Quantum dots	Superior optical stability, suitable for multi-modal detection, designed to target specific tissue, potential cytotoxity (required encapsulation).[64_66]	Diffusion in to lens in vitro. [67]
Nanoshells	Good contrast agents for OCT imaging.[68]	Gold nanoshells to enhance tissue contrast.[69]
Gold nanoparticles	Good contrast agents, RES uptake.[70]	TNF-gold nanoparticles for tumor targeting.[71]
Magnetic nanoparticles	Good MRI contrast property.	In vitro use only.[72]