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A Paradigm Shift in Ocular Drug Delivery to Posterior Segment: Review on Current Drug Delivery Approaches

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Objectives: Owing to the increasing number of patients suffering from posterior eye disorders, efficient medicine delivery to the posterior segment is now in great demand in the clinical services. With unmet medical requirements, the posterior eye segment is an important therapeutic target. So, physicians should be informed of new indications and current strategies of drug delivery when new technologies enter the market.
Summary: The most common causes of vision impairment in developed nations are abnormalities of the posterior eye tissues. Poor drug distribution to lesions in patient's eyes is a key barrier to ocular disease therapy. The existence of barriers, such as the corneal barrier, aqueous barrier, and inner and outer blood-retinal barriers, severely limits medication accessibility in these locations. Because of its anatomical peculiarities, the posterior portion is particularly difficult to access for medications. The use of several new strategies for drug delivery is therefore a viable option for enhanced therapy of ocular disorders since recent advances in ocular drug delivery systems research have brought fresh insights into drug development.
Conclusion: This article provides an overview of several aspects of ocular medication

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administration to the posterior region, with a focus on nano carrier-based approaches, suprachoroidal drug delivery system and ophthalmic devices, including the structure of the eye, its barriers, delivery routes, and the present status of drugs/devices.

Keywords: Ocular delivery; nanoparticles; posterior segment; retinal barriers.

1. INTRODUCTION

Pharmaceutical scientists are faced with one of the most appealing and hard endeavours: ophthalmic medication delivery. The eye is a multi-compartmental, tiny organ. Its anatomy, physiology, and biochemistry made it highly impervious to xenobiotics [1].

Of the total ocular diseases, 55% are posterior segment diseases, while these diseases may lead to permanent vision loss if left untreated. The number of diseases affecting the posterior eye segment is expanding at an alarming rate [2]. In industrialized countries, posterior segment ocular disorders are the most common cause of vision impairment. These diseases include, for example, age-related macular degeneration and diabetic retinopathy [3].

Over the last few decades, significant progress has been made in research, particularly in the development of advanced drug delivery systems aimed at delivering ocular therapeutics to target sites in an optimized and controlled manner, either by increasing penetration across mucosa or by extending the contact time of the carrier with the ocular surface. Emerging new controlled drug delivery systems such as dendrimers, microemulsions, mucoadhesive polymers, hydrogels, iontophoretic drug delivery, laser therapy along with sclera plugs, non-viral gene therapy, stem cells technology, and s-RNA based approaches are also developed. Advancement in material sciences and formulations has provided new exciting possibilities to deliver drugs to the posterior segment of the eye as well [1].

This review will give an update on recent case reports and updates on the recent progress and trends in ocular drug delivery systems.

1.1 The Anatomy and Physiology

The human eye is a globular structural organ that is around 24 mm in diameter. It generates a 3D mobile image that is frequently colored in natural light. The retina's cone cells and rod cells aid in light detection and visual perception. Colors can be distinguished and depth perception can be discerned. It is divided into two sections: the anterior and posterior regions [4]. The eyeball is made up of three translucent layers: the outer coat, the tunica media, and the intima. The sclera is a tough tissue that runs from the back of the eye to the front, producing the cornea, which is transparent. The uveal coat in the middle is primarily made up of cribriform tissue that is densely vascularized and pigmented, and it is separated into three sections: the iris in front, the choroid in the back, and the ciliary body in between. The visual receptor is hidden behind the retina, which is a highly specialized neuronal membrane. In front of the ciliary body, it atrophies [5].

The cornea, which is roughly 0.5 mm thick and 11.5 mm in diameter, is connected to the larger posterior part, which includes the retina, vitreous humor, choroid, and the outermost white shell known as the sclera, by a distinct curve. With a diameter of around 24 mm, the posterior component makes up the remaining five-sixths [6]. The limbus is a connective tissue that connects the sclera and cornea. The iris is the pigmented framework around the eye center and the darkly colored pupil. The iris dilator and muscles in the sphincter govern the size of the pupil, which controls the amount of light that enters the eyes [1].

1.2 Ocular Pharmacokinetics: Barriers in Drug Delivery

Drugs can be administered locally or systemically to reach the ocular tissues. Drugs can't get to their targets because of tissue barriers (Fig. 1). The ocular surface is protected by corneal and conjunctival epithelial barriers. The blood-aqueous barrier, which is made up of uveal capillary endothelia and ciliary epithelia, prevents chemicals from entering the anterior chamber from the systemic circulation, whereas the blood-retina barrier prevents drug diffusion from the systemic blood into the retina and vice versa. The outer and inner blood-retina barriers, created by the retinal pigment epithelium (RPE) and the

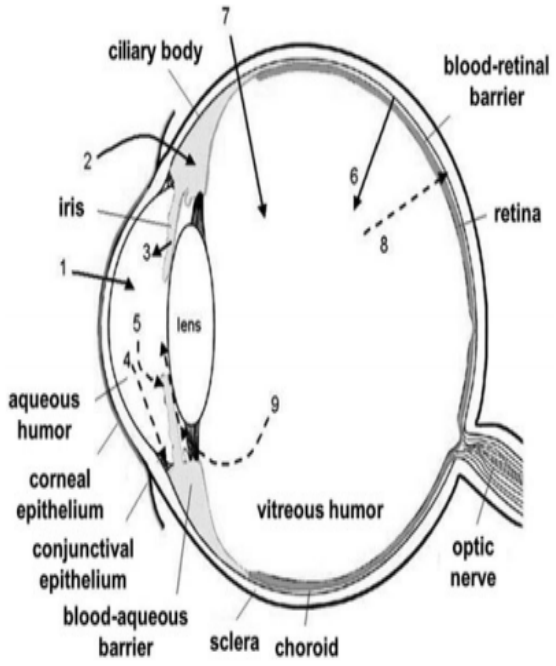

Fig. 1. Structure of eye

(1) Trans-corneal permeation from the lachrymal fluid into the anterior chamber, (2) noncorneal permeation across conjunctiva and sclera into anterior uvea, (3) distribution of drug from the bloodstream through the blood-aqueous barrier into the anterior chamber, (4) drug elimination from the anterior chamber by aqueous humor passage into the trabecular meshwork and canal of Schlemm, (5) elimination of the drug from aqueous humor into the systemic circulation across the blood-aqueous barrier, (6) distribution of drug from blood into posterior eye across the blood-retina barrier, (7) intravitreal drug administration, (8) elimination of drug from vitreous through the posterior route across the blood-retina barrier, and (9) drug from vitreous through anterior route to the posterior chamber.

tight retinal capillary walls, respectively, make up the barrier [3]. The physicochemical features of the medication, its removal from the lacrimal fluid, corneal barriers, and non-corneal absorption are the key obstacles and deciding variables in ocular drug delivery. The route and rate of penetration in the cornea are further affected by lipophilicity, solubility, molecule size and shape, charge, and degree of ionization. The penetration of ionizable drugs, such as weak acid and weak bases, is influenced by the chemical balance between ionized and unionized drugs.

Tight junctions act as a selective barrier for tiny molecules, preventing macromolecules from diffusing through the paracellular pathway. The rate-limiting barrier for ocular absorption of most lipophilic medicines is the hydrophilic corneal stroma. Topically administered ocular medications that are not absorbed by the corneal pathway may be absorbed by non-corneal routes, resulting in drug loss at the targeted spot [1].

Tears consist of proteins and mucins that attach to drug molecules, lowering the effective concentration of medication in contact with the cornea. This has a detrimental impact on drug bioavailability.

The blood-aqueous and blood-retina barriers are the two primary barriers in the intraocular environment. These two components prevent molecules from penetrating the eye chamber, resulting in ineffective intraocular tissue treatment [6].

The blood-ocular barrier (BOB) has three major purposes: it keeps infections out of the eye, regulates tissue/fluid composition, and creates aqueous- humor. The blood-aqueous barrier is formed by tight junctions at the level of the iris vascular epithelium and non-pigmented ciliary epithelium, while the blood-retinal barrier is formed by tight junctions at the retinal pigment epithelium (RPE) and vascular endothelium levels [7] The BOB not only prevents germs from entering the eye but also prevents medications from entering. Surgery, uveitis, diabetes, and ocular infection, as well as specific therapies like photocoagulation and cryopexy, can all compromise this barrier. When the BOB fails, medicines can more readily enter and exit the eye; Starling forces (forces that govern fluid balance) can change, producing macular edema; and serum can leak into the eye, causing cellular proliferation and aqueous hyposecretion [8].

1.3 Route of Administration

Table 1. Advantages of various ocular routes of drug administration for posterior segment related diseases

Route of administration	Advantages
Topical	Non-invasive, patient compliant
Systemic/intravenous	Less frequency of administration
Oral	Non-invasive, patient compliant
IVT	Less frequent dosing, depot action, and a direct local and long-lasting pharmacologic impact
Trans-scleral	Less invasive, easier to reach, vast surface area, suitability and comparatively greater permeability for both small and big compounds, depot action, large dosage administration, less adverse effects than IVT, no obstruction in the optic path
Suprachoroidal	Less invasive, depot action, direct impact on the choroid and outer RPE, favourable for small molecules, low systemic level of medication, lesser risk of adverse effects than IVT, no obstruction in the optic route

1.4 Strategies for Delivering Drugs to the Posterior Segment

There are three techniques of delivering medications to the eye from a conceptual standpoint:

1. Distribute vast amounts of medicines throughout the body

Drugs are usually given systemically in doses that are theoretically large enough to reach therapeutic levels in the eye. In reality, however, the BOB limits the number of medications that reach the posterior segment, necessitating systemic administration of extremely large dosages to obtain even borderline therapeutic retinal drug levels. The systemic toxicity related to the relatively high systemic medication levels required to overcome the BOB is typically a limiting issue in this strategy.

2. Introduce modifications to the BOB

Modifying the permeability of the BOB to allow better drug penetrance and access to specific medications and substances [e.g., histamines, bradykinin agonists, and vascular endothelial growth factor (VEGF)] that can enhance vascular permeability is the second route to drug administration. This method is rarely employed.

3. Drugs are delivered locally to the eye

The third technique entails delivering medications to the target tissues on a local level. There is evidence that local medication delivery to the posterior segment is the most successful technique for treating posterior segment disorders, and this is the strategy that is most usually employed in clinical practice [8].

2 CURRENT STATUS

Ocular drug delivery devices designed to maintain drug release are now available on the market or in clinical studies. The majority of them are used to treat long-term disorders of the eye's posterior portion. Macular degeneration, viral infections (such as CMV infections), glaucoma, ocular inflammations, dry eye syndrome, and retinal degenerations are all key indications for ocular drug delivery systems. The goal is to create a system that has increased ocular medication absorption and activity duration while posing a low risk of ocular problems.

2.1 Ocular Drug Delivery to Date

2.1.1 Implants

Implants are effective drug delivery systems for chronic ocular diseases. Implants once adjusted, in the eye, prolonged the drug residence time to an appropriate time. They are commonly used for the treatment of ocular disorders such as cytomegalovirus (CMV) retinitis which is an ocular infection occurs in AIDS patient and one of the leading to blindness. Earlier, non-biodegradable polymers were used but they needed surgical procedures for insertion and removal but now the trend has been changed to biodegradable ones. Biodegradable polymers such as PLA are safe and effective to deliver

drugs in the vitreous cavity and show no toxic signs when inserted [7].

The implants have the advantages of (1) bypassing the blood–ocular barriers to delivering constant therapeutic levels of drug directly to the site of action, (2) avoiding the side effects associated with frequent systemic and intravitreal injections, and (3) requiring a smaller amount of drug during treatment [9]. The implants are always implanted intravitreally, in the pars plana of the eye (posterior to the lens and anterior to the retina), for intraocular delivery, which necessitates minimal surgery, some of the FDA approved implants are mentioned in Table 2 [3].

2.1.2 Microspheres

The medicament will be encapsulated in microparticles (1–1000 mm) or nanoparticles (1–1000 nm) using this carrier technology. Polymers that are biodegradable and biocompatible, such as polylactide and PLGA, which have both been approved by the FDA, are employed. These methods are primarily implanted through intravitreal injection, which is a less invasive method than surgery. They provide drugs for weeks or even months at a time, reducing the number of injections required [2]. Intravitreal injections of particle systems have the potential to produce vitreal clouding. Microparticles, on the other hand, tend to settle to the bottom of the vitreal cavity, but nanoparticles are more likely to induce clouding in the vitreous. It has been documented how erodible, non-erodible, and lipid microspheres can be used for ocular administration. In the polymer matrix, the drug is uniformly spread (monolithic system). As a result, the drug-loaded microparticles are suspended in a liquid carrier medium, which may also include the drug [10].

Sridhar Duvvuri et al., (2007) observed an ideal in vitro release of encapsulated ganciclovir was obtained by physically mixing microspheres prepared from different polymer blends before its dispersion in the thermo-gelling polymer. The formulation maintained mean vitreal concentrations of ganciclovir at approximately 0.8 micron/mL for 14 days, whereas direct injections could maintain drug levels above 0.8 microns/mL for 54 h only [11].

Rocío Herrero-Vanrell et al. (2014) microspheres prepared from PLA and PLGA biomaterials are well tolerated after periocular and intravitreal injections in animals and humans. PLA and PLGA microspheres aggregate after injection, acting as an implant. Biodegradable microspheres might be useful in retinal healing in regenerative medicine [12].

Javier Rodríguez Villanueva et al., (2016) described an efficient and reproducible method for encapsulating Dexamethasone in biodegradable PLGA (50:50) microspheres [13].

Table 2. Implants approved for posterior segment disorder treatment

Implants	current status	Description
Vitrasert	FDA approved in 1996	Ganciclovir-containing non-biodegradable polymer implant for the treatment of cytomegalovirus (CMV) retinitis. The drug is released for up to eight months.
Retisert	FDA approved in 2005	For the treatment of chronic non-infectious posterior uveitis, a non-biodegradable polymer implant containing fluocinolone acetonide is used. Fluocinolone is released for up to 2.5 years.
Ozurdex (formerly Posurdex®)	FDA approved in 2009	For the treatment of macular edema, the first biodegradable polymer implant containing dexamethasone was developed. A 22-gauge needle is inserted into the vitreous to release the medication for up to six months.
Iluvien (formerly Medidur®)	FDA approved in 2014	For the treatment of diabetic macular edema, a non-biodegradable implant containing fluocinolone acetonide is used. A 25-gauge needle is inserted into the vitreous to release the medication for up to three years.
Yutiq	FDA approved in 2018	It is a corticosteroid intravitreal implant indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

2.1.3 Nano-particulates for drug delivery

2.1.3.1 Lipid nanoparticles

Three types of lipid nanoparticles, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and hybrid lipid nanoparticles are often used in the studies. The former two nanoparticle systems typically form a solid lipid core and have the capability of loading both lipophilic drugs and hydrophilic drugs into the lipid matrix. SLN is strictly made up of more than one solid lipids, whose melting point is above 40°C. SLN shows the advantages of controlled release dating from the early 1990s [14], reduced toxicity for cells, high compatibility, and in vivo tolerability [15]. NLC containing liquid lipids and solid lipids in their components appear with the advantages of higher drug-loading capacity, better stability during storage, and improved release properties compared to SLN. Nevertheless, hybrid lipid nanoparticles modified by multifunctional polymers [16], combine the merits of polymeric nanoparticles and lipid-based systems, which simultaneously improve pharmacokinetics and biodistribution of the loaded drug.

Patrizia Chetoni et al. (2016) discovered that following ocular and intravenous administration of Tobra-SLN formulations, drug concentrations were considerably greater in all ocular tissues compared to reference formulations, and only Tobra-SLN permitted drug penetration into the retina. The current work adds to our understanding of the utilization of SLN as carriers for ocular medication transport to the posterior chamber and might lead to novel treatment options for ocular infections, as well as a strategy to combat microbial resistance [17].

Balguri et al., (2017) successfully prepared indomethacin (IN)-loaded lipid nanoparticles (IN-SLN, IN-CS (chitosan chloride)-SLN and IN-NLC) by a hot homogenization method. Then the disposition of IN from these topically administered formulations to the posterior eye was evaluated [18].

Joana Araújo et al., (2011) study is about Triamcinolone acetonide (TA) which is a corticosteroid drug currently administered by intravitreal injection for a broad spectrum of inflammatory, edematous, and angiogenic ocular diseases. To increase the drug's bioavailability by ocular instillation, TA was encapsulated in nanostructured lipid carriers (NLC), previously optimized by their group using a factorial design approach [19].

2.1.3.2 Nanoparticles

Polymeric nanoparticles of colloidal nanosized systems (1 nm<d<1000nm) are ideally appropriate for ocular medication administration to the required locations due to the variety of polymers in their compositions [20]. Because of their structural differences, polymeric nanoparticles are divided into nanospheres and nano-capsules. Nanospheres have a polymeric matrix with three drug-loading options: (1) encapsulating medicines in the spheres, (2) absorbing drugs on the surface, and (3) dispersing medications throughout the polymeric network. In contrast, the drug-loading forms of core-shell nano-capsules are restricted to dissolve drugs in the core or absorb medications on the shell [21]. The polymers utilized in the nanoparticles are natural materials or modified ones, such as natural materials chitosan, dextran sulfate, hyaluronic acid, and synthetic polymers poly (lactic acid) (PLA), poly(lactic-co-glycolic-acid) (PLGA), poly(ε-caprolactone). The polymeric nanoparticles can enhance the pre-cornea retention period and are biocompatible and biodegradable for ocular application. Furthermore, to employ polymers in ocular medication administration, it is critical to assess their potential toxicity [22].

Wai-Leung Langston Suen et al., (2013) presented folate-decorated polymeric nanoparticles as carriers for poorly soluble therapeutic compounds to be delivered intracellularly and for a long time to RPE cells. Internalization of these nanoparticles into ARPE-19 (human RPE cell line) via receptor-mediated endocytosis resulted in considerably greater cellular absorption than particles without folate treatment. Triamcinolone acetonide (TA) was successfully encapsulated (>97%) within the folate-decorated nanoparticles and slowly released over 4 weeks at pH 5.5 and 8 weeks at pH 7.4 [23].

Sulabh P Patel et al., (2015) investigated the design, synthesis, and application of novel biodegradable and biocompatible Penta block (PB) copolymers, i.e., polyglycolic acid-polycaprolactone-polyethylene glycol-polycaprolactone-polyglycolic acid (PGA-PCL-PEG-PCL-PGA) and polylactic acid-polycaprolactone-polyethylene glycol-

polycaprolactone-polylactic acid (PLA-PCL-PEG-PCL-PLA) for sustained protein delivery [24].

Naba Elsaid et al., (2016) analysed the effects of incorporating chitosan-based nanoparticles containing ranibizumab within the PLGA microparticles on the loading, stability, activity, and release of the ranibizumab, as well as their effects on the physicochemical properties of the PLGA microparticles [25].

2.1.3.3 Liposomes

Liposomes are self-assembled vesicles and form when lipid materials are dispersed in an aqueous medium. The nanosized liposomes are made up of phospholipid bilayers with aqueous units that can transport both hydrophilic and hydrophobic medicinal molecules to the target locations [22]. The biocompatible phospholipids used to formulate liposomes mainly include phosphatidylserine (PS), soya phosphatidylcholine, phosphatidylcholine (PC), and phosphatidylethanolamine, which are similar to the lipid on the cell membrane and could enhance pre-corneal permeation [26].

The very next generation liposome, which has been engineered with mucoadhesive and penetration-enhancing polymers, may not only entrap drug molecules but also target specific locations on the cornea by adhering to the surface [27].

Hirofumi et al., (2012) prepared diclofenac-loaded multilamellar liposomes that are modified by polyvinyl alcohol (PVA 205) and polyvinyl alcohol derivatives (PVA-R) through the calcium acetate gradient method for the first time [28].

T Lajunen et al. (2014) developed methods of liposome preparation utilizing a microfluidizer to achieve adjustable nanoparticle size (even less than 80 nm) and high loading capacity of plasmid DNA [29].

K Pachis et al. (2017) effectively introduced a new Flurbiprofen (FLB)-in-liposome-in-hydrogel formulation as a strategy to prolong FLB release and boost ocular bioavailability after intravitreal injection. FLB loading into liposomes was improved for this, and liposomes were entrapped in Pluronic F-127 thermosensitive hydrogels (P) [30].

2.1.3.4 Nano micelles

Nano micelles are colloidal drug delivery devices that may entrap therapeutic chemicals at their core and self-assemble in a solution. They are formed up of amphiphilic surfactants or block copolymers and range in size from 10 to 200 nm. When the concentration of polymers in a solution exceeds a certain concentration known as the critical micellar concentration (CMC), nano micelles form instantly. Because of hydrophobic interactions, nano micelles can encapsulate hydrophobic medicines in the hydrophobic core of the micelles. While the hydrophilic corona interacts with the external aqueous fluid, a somewhat lipophilic drug's solubility is increased. This colloidal dosage form may be used to make clear aqueous solutions that may be used as eye drops. Surfactant nano micelles and polymeric nano micelles are two types of nano micelles [31].

TRavi D. Vaishya et al. (2014) created polymeric nano micelles encapsulated with dexamethasone (DEX). Ex vivo permeability and stiff nano micelle core results suggest that these nano micelles might carry DEX and other hydrophobic anti-inflammatory drugs like rapamycin to the back of the eye via a topical route for the treatment of intermediate to posterior segment uveitis [32].

2.1.4 Iontophoresis

Many medicines, including fluorescein, hormones, antibiotics, antivirals, and macromolecules, have been demonstrated to promote transscleral permeability using iontophoresis. It is a non-invasive approach that uses a tiny electric current to increase the penetration of an ionized medication into the tissue [5]. With negligible side effects, transscleral iontophoresis delivers large concentrations of the administered medicine to the choroid and retina. Epithelial edema, a reduction in endothelial cells, inflammatory infiltration, and burns are all side effects of iontophoresis, the severity of which varies depending on the place of application, current density, and duration. Iontophoresis has been proven to harm the choroid and destroy retinal layers at greater current densities [7].

S Pescina et al. (2013) investigated in vitro trans-scleral iontophoresis of methylprednisolone hemisuccinate using concentrated drug solutions and short application times to mimic the iontophoretic conditions of in vivo studies [33].

Verena Santer et al. (2018) investigated short duration transscleral iontophoretic delivery of four triamcinolone acetonide (TA) amino acid ester prodrugs (TA-AA) (alanine, Ala; arginine, Arg;

isoleucine, Ile and lysine, Lys) using whole porcine eyes globes in vitro. When compared to passive diffusion, transscleral iontophoresis (3 mA/cm2 for 10 min) boosted the overall drug distribution of the TA-AA prodrugs by 14-30 times. The study added to the growing body of data that transscleral iontophoresis has the potential to treat posterior segment inflammatory disorders non-invasively [34].

3. CURRENT STRATEGIES

IVT injections and implants, as well as systemic intravenous injections, are now the most common methods of delivering medications to the posterior portion of the eye. Elevated VEGF, depleted antioxidants, and inflammation are reported to be key culprits in most posterior segment disorders such as DR, RVO, DME, AMD, CNV, CMV retinitis, and so on.

3.1 Intravitreal Injections of Anti-VEGF Agents

The earliest mention of VEGF in ophthalmology is from 1940 when a group of scientists claimed that a diffusible factor was responsible for proper vasculature development. In proliferative diabetic retinopathy, an imbalance in the particular factor resulted in neovascularization (DR). VEGF was discovered to be a possible mediator of choroidal and intraocular neovascularization in individuals with age-related macular degeneration in the late 1990s (AMD).

In numerous animal models, proof of concept studies showed that VEGF blockade inhibited neovascularization, indicating that VEGF blockade might be a possible new method to overcome retinal illnesses involving neovascularization [8].

Xiangke Yin et al. (2019) developed RFP (DAVP2 and DAVP3) showed suppression of endothelial cell migration and proliferation and, inhibition of angiogenesis in a laser-induced choroidal neovascularization mouse model after intravitreal injections by inhibiting not only VEGF but also platelet-derived growth factor through suppression of the phosphorylation activation processes in the metabolic cascade [35].

In a study conducted by *Raquel Lima e Silva* et al. (2017), a collagen IV-derived peptide called "AXT 107" was produced, which functioned by coupling to VEGF and platelet-derived growth factor receptors. In many in vivo studies, it suppressed subretinal and retinal neovascularization [36].

3.2 Suprachoroidal Drug Delivery Through Hollow Microneedles

The delivery of treatments in the suprachoroidal region has shown promise in terms of delivering therapeutic drugs at a higher concentration to the target tissue (retina and choroid). Anatomical investigations indicating the diffusion of therapeutic substances following drug application at the suprachoroidal space support this theory.

Patel et al., (2012) demonstrated suprachoroidal drug delivery through the posterior pars plana of a rabbit model using a hollow microneedle. The suprachoroidal drug delivery was a minimally invasive procedure demonstrating safe delivery into the retina and choroid with no adverse effects [37].

Jae Hwan Jung et al. (2019) investigated suprachoroidal space (SCS) injection formulation with collagenase to improve drug delivery coverage and boost posterior drug targeting inside SCS by breaking down collagen fibrils that connect the sclera and choroid in the SCS [38].

3.3 Ophthalmic Devices

Due to its efficacy in restoring normal visual acuity, ocular implants and medication delivery systems have attracted a lot of attention in recent years [9]. These devices can be non-biodegradable, biodegradable, or stimuli-responsive systems that are implanted into the eye for drug delivery or to repair a defect. Drug delivery systems have become more important in recent years as a result of their capacity to administer medicine or drug in a regulated and sustained way for both the anterior and posterior segments of the eye [39]. The following ophthalmic equipment which are given in Table 3 are extremely important in the diagnosis, treatment, and monitoring of posterior segment illnesses [40].

3.4 Nano-formulations

Nanotechnology has infiltrated every facet of medicine, and ocular therapies cannot be left behind. Liposomes, microspheres, dendrimers, and other nano-formulations have been used to treat illnesses of the posterior portion of the eye

Table 3. Recent ophthalmic devices in pipeline for posterior segment treatment

Device	Status	Description	Benefits
Yutiq	FDA approved in 2018	It's an intravitreal micro insert that isn't bio-erodible.	It offers convenience because it can be injected with a small-gauge needle.
GB-102 Other Name: Sunitinib malate	Phase 2 trails	It encapsulates sunitinib malate within bioabsorbable microparticles	It allows us to provide a more sustainable treatment strategy.
AR-1105	Phase 2 trails	It is a bio-erodible implant that is injected intravitreally.	It offers 6 months duration of sustained efficacy, improved administration due to smaller needle size, and possibly a better safety profile due to lower peak drug levels.

Table 4. Current potential nanotechnology strategies for treatment of posterior segment disorders

Nano-formulations	Drug/ingredients	Output	Reference
Solid Lipid Nanoparticles	Lipid-polyethylene glycol matrix solid lipid nanoparticles Fluconazole	FCZ-SLN effectiveness was not harmed by encapsulation within SLNs or gradual release. The developed system was safe and stable (even after autoclaving), with ideal viscosity, refractive index, and osmotic pressure.	Shilpa Kakkar et al., (2021) [43]
Microsphere	Glial cell line-derived neurotrophic factor-GDNF and Tauroursodeoxycholic acid-TUDCA	The in vitro release of these optimized microparticles was sustained for 91 days. These findings indicate that the microencapsulation process used in this study is a potential technical technique for developing multi-loaded intraocular medication delivery devices (IODDS).	Alicia Arranz-Romera et al., [44]
Nano-Structured Lipid Carriers	Dexamethasone	At 34.4°C, NLCs-gel showed a quick sol-gel transition and nano-sized, narrowly scattered particles. NLCs-gel enhanced ocular bioavailability by lengthening precorneal retention time and enhancing corneal permeability, according to Ritger-Peppas corneal penetration trials.	Zhenjie Mo et al., [45]
Liposomes	Triamcinolone acetonide	When administered on the ocular surface, a topical ophthalmic TA-loaded liposomes formulation (TALF) was intended to transport TA into the posterior section of the	Jose Navarro-Partida et al., [46]

Nano-formulations	Drug/ingredients	Output	Reference
		eye. In either of the animal or clinical tests, no inflammation, lens opacity, edema, or rise in intraocular pressure was seen following the instillation of TALF.	
Nanoparticles	Dorzolamide and Dexamethasone	γ-cyclodextrin (γ-CD)-based nanoparticle aggregates were used to create eye drop formulations. This technique has the potential to be utilized with various types of pharmacological molecules and to replace or augment invasive treatments, resulting in safer, non-invasive medicines that may be self-administered as eye drops by patients, particularly for posterior segment diseases.	Thorsteinn Loftsson et al., [47]
	Resveratrol	The suggested formulation revealed potential cellular uptake and anti-angiogenic properties by reducing VEGF expression in vitro, according to cellular uptake and VEGF expression levels for the created nanoparticles. The findings demonstrated that resveratrol-loaded nanoparticles might be utilized alone or in combination with anti-VEGF agents to treat neovascular AMD.	Priyanka Bhatt et al., [48]
	Fluocinolone acetonide (FA) and PLGA nanoparticles	FA was released continuously from the NPs for 30 days in an in vitro drug release investigation.	Joyce Pinto et al., [49]
Nano micelles	Everolimus	When compared to everolimus suspension, the nano micelles were shown to have a high encapsulation efficiency and result in the prolonged release of everolimus. The penetration of everolimus nano micelles over goat cornea was substantially greater than that of everolimus suspension (p0.001).	Nikita Mehra et al., [50]

[41]. Enhanced penetration and retention, bypass of the reticuloendothelial system, fast internalization, and biocompatibility are just a few of the benefits they provide. For regulated and sustained drug administration via diverse channels, several bio-degradable, tunable polymers and lipids are being studied [42]. Many nano-formulations, such as nanostructured lipid carrier (NLC), liposome, NP, emulsion, are being tested preclinically for drug delivery to the posterior portion of the eye and are showing promising results (7). These nano-formulations are currently being used to have a favorable influence on biological molecules (peptide, protein, gene, oligonucleotide, monoclonal antibody, etc.), starting with delivering synthetic chemical moieties to target tissue. Current potential nanotechnology strategies for treatment of posterior segment disorders are detailed in the Table 4.

4. CONCLUSION

Intricate structure and physiology of the eye, recommends local treatment for eye illness. Disorders associated with the anterior segment of the eye are usually treated with topical formulations such as eye drops, ointments, ocular inserts, etc. Whereas, chronic disorders affecting the posterior segment need specific treatment other than topical formulations, as they are ineffective in this case, thus enabling the need for a new DDS.

In this review article, we investigated new DDS with several strategies that showed potential enhancement in the treatment of posterior segment disorders. Nanotechnology-based formulations with improved penetration and retention for efficient long-term drug release have been reported. Ophthalmic devices offer convenience and sustained efficacy in restoring normal visual acuity. Intravitreal injections of Anti-VEGF Agents showed VEGF blockade to overcome retinal illnesses involving neovascularization whereas Suprachoroidal Drug Delivery through hollow microneedles boost posterior drug targeting inside SCS and showed promising delivery of therapeutic drugs at a higher concentration into the retina and choroid demonstrating safe delivery with no adverse effects.

Longer-acting medication administration and good long-term illness control are now possible thanks to technological advancements. Greater target specificity, potentially real-time monitoring of active drug levels, and reciprocal dosage changes will be possible with future devices.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wadhwa S, Paliwal R, Paliwal SR, Vyas SP. Nanocarriers in ocular drug delivery: An update review. 2009;15.
DOI: 10.2174/138161209788923886
2. Wang Y, Xu X, Gu Y, Cheng Y, Cao F. Recent advance of nanoparticle-based topical drug delivery to the posterior segment of the eye. Expert Opin Drug Deliv. 2018;15(7):687-701.
DOI: 10.1080/17425247.2018.1496080
3. del Amo EM, Urtti A. Current and future ophthalmic drug delivery systems. A shift to the posterior segment. Drug Discov Today. 2008;13(3-4):135-143.
DOI: 10.1016/j.drudis.2007.11.002
4. Wang H, Sun M. Promising approach in the treatment of glaucoma using nanotechnology and nanomedicine-based systems. molecules. 2019;24(3805).
DOI: 10.3390/molecules24203805
5. Achouri D, Alhanout K, Piccerelle P, Andrieu V. Recent advances in ocular drug delivery. Drug Dev Ind Pharm. 2013;39(11):1599-1617.
DOI: 10.3109/03639045.2012.736515
6. Weng Y, Liu J, Jin S, Guo W, Liang X, Hu Z. Nanotechnology-based strategies for treatment of ocular disease. Acta Pharm Sin B. 2017;7(3):281-291.
DOI: 10.1016/j.apsb.2016.09.001
7. Nayak K, Misra M. A review on recent drug delivery systems for posterior segment of eye. Biomed Pharmacother. 2018;107: 1564-1582.
DOI: 10.1016/j.biopha.2018.08.138
8. Moisseiev E, Loewenstein A. Drug delivery to the posterior segment of the eye. Dev Ophthalmol. 2017;58:87-101.
DOI: 10.1159/000455276
9. Yasin MN, Svirskis D, Seyfoddin A, Rupenthal ID. Implants for drug delivery to the posterior segment of the eye: A focus on stimuli-responsive and tunable release systems. J Control Release. 2014;196: 208-221.
DOI: 10.1016/j.jconrel.2014.09.030
10. Joshi A. Microparticulates for ophthalmic drug delivery. J Ocul Pharmacol. 1994; 10(1):29-45.
DOI: 10.1089/jop.1994.10.29

11. Duvvuri S, Janoria KG, Pal D, Mitra AK. Controlled delivery of ganciclovir to the retina with drug-loaded poly(D,L-lactide-co-glycolide) (PLGA) microspheres dispersed in PLGA-PEG-PLGA gel: A novel intravitreal delivery system for the treatment of cytomegalovirus retinitis. J Ocul Pharmacol Ther. 2007;23(3).
DOI: 10.1089/jop.2006.132
12. Herrero-Vanrell R, Bravo-Osuna I, Andrés-Guerrero V, Vicario-de-la-Torre M, Molina-Martínez IT. The potential of using biodegradable microspheres in retinal diseases and other intraocular pathologies. Prog Retin Eye Res. 2014;42.
DOI: 10.1016/j.preteyeres.2014.04.002
13. Rodríguez Villanueva J, Bravo-Osuna I, Herrero-Vanrell R, Molina Martínez IT, Guzmán Navarro M. Optimising the controlled release of dexamethasone from a new generation of PLGA-based microspheres intended for intravitreal administration. Eur J Pharm Sci. 2016;92.
DOI: 10.1016/j.ejps.2016.03.012
14. Souto EB, Doktorovová S. Solid lipid nanoparticle formulations. pharmacokinetic and biopharmaceutical aspects in drug delivery. Methods Enzymol. 2009;464(C).
DOI: 10.1016/S0076-6879(09)64006-4
15. Doktorovova S, Souto EB, Silva AM. Nanotoxicology applied to solid lipid nanoparticles and nanostructured lipid carriers - A systematic review of in vitro data. Eur J Pharm Biopharm. 2014;87(1).
DOI: 10.1016/j.ejpb.2014.02.005
16. Das S, Ng WK, Tan RBH. Are nanostructured lipid carriers (NLCs) better than solid lipid nanoparticles (SLNs): Development, characterizations and comparative evaluations of clotrimazole-loaded SLNs and NLCs? Eur J Pharm Sci. 2012;47(1).
DOI: 10.1016/j.ejps.2012.05.010
17. Chetoni P, Burgalassi S, Monti D, et al. Solid lipid nanoparticles as promising tool for intraocular tobramycin delivery: Pharmacokinetic studies on rabbits. Eur J Pharm Biopharm. 2016;109.
DOI: 10.1016/j.ejpb.2016.10.006
18. Balguri SP, Adelli GR, Tatke A, Janga KY, Bhagav P, Majumdar S. Melt-cast noninvasive ocular inserts for posterior segment drug delivery. J Pharm Sci. 2017;106(12).
DOI: 10.1016/j.xphs.2017.07.017
19. Araújo J, Nikolic S, Egea MA, Souto EB, Garcia ML. Nanostructured lipid carriers for triamcinolone acetonide delivery to the posterior segment of the eye. Colloids Surfaces B Biointerfaces. 2011;88(1).
DOI: 10.1016/j.colsurfb.2011.06.025
20. Ghanghoria R, Tekade RK, Mishra AK, Chuttani K, Jain NK. Luteinizing hormone-releasing hormone peptide tethered nanoparticulate system for enhanced antitumoral efficacy of paclitaxel. Nanomedicine. 2016;11(7).
DOI: 10.2217/nnm.16.19
21. Meyer H, Stöver T, Fouchet F, et al. Lipidic nanocapsule drug delivery: Neuronal protection for cochlear implant optimization. Int J Nanomedicine. 2012;7.
DOI: 10.2147/IJN.S29712
22. Wang Y, Xu X, Gu Y, Cheng Y, Cao F. Recent advance of nanoparticle-based topical drug delivery to the posterior segment of the eye. Expert Opin Drug Deliv. 2018;15(7):687-701.
DOI: 10.1080/17425247.2018.1496080
23. Suen WLL, Chau Y. Specific uptake of folate-decorated triamcinolone-encapsulating nanoparticles by retinal pigment epithelium cells enhances and prolongs antiangiogenic activity. J Control Release. 2013;167(1).
DOI: 10.1016/j.jconrel.2013.01.004
24. Patel SP, Vaishya R, Pal D, Mitra AK. Novel pentablock copolymer-based nanoparticulate systems for sustained protein delivery. AAPS PharmSciTech. 2015;16(2).
DOI: 10.1208/s12249-014-0196-6
25. Elsaid N, Jackson TL, Elsaid Z, Alqathama A, Somavarapu S. PLGA microparticles entrapping chitosan-based nanoparticles for the ocular delivery of ranibizumab. Mol Pharm. 2016;13(9).
DOI: 10.1021/acs.molpharmaceut.6b00335
26. Peptu C, Popa M, Savin C, Popa R, Ochiuz L. Modern drug delivery systems for targeting the posterior segment of the eye. Curr Pharm Des. 2015;21(42).
DOI: 10.2174/1381612821666151027151847
27. F Fangueiro J, Veiga F, M Silva A, B Souto E. Ocular drug delivery - New strategies for targeting anterior and posterior segments of the eye. Curr Pharm Des. 2016;22(9).
DOI: 10.2174/1381612822666151216145900
28. Fujisawa T, Miyai H, Hironaka K, et al. Liposomal diclofenac eye drop formulations targeting the retina: Formulation stability improvement using

surface modification of liposomes. Int J Pharm. 2012;436(1-2).
DOI: 10.1016/j.ijpharm.2012.07.024

29. Lajunen T, Hisazumi K, Kanazawa T, et al. Topical drug delivery to retinal pigment epithelium with microfluidizer produced small liposomes. Eur J Pharm Sci. 2014;62.
DOI: 10.1016/j.ejps.2014.04.018
30. Pachis K, Blazaki S, Tzatzarakis M, et al. Sustained release of intravitreal flurbiprofen from a novel drug-in-liposome-in-hydrogel formulation. Eur J Pharm Sci. 2017;109.
DOI: 10.1016/j.ejps.2017.08.028
31. Vaishya RD, Gokulgandhi M, Patel S, Minocha M, Mitra AK. Novel dexamethasone-loaded nanomicelles for the intermediate and posterior segment uveitis. AAPS PharmSciTech. 2014;15(5).
DOI: 10.1208/s12249-014-0100-4
32. Vaishya RD, Gokulgandhi M, Patel S, Minocha M, Mitra AK. Novel dexamethasone-loaded nanomicelles for the intermediate and posterior segment uveitis. AAPS PharmSciTech. 2014;15(5):1238-1251.
DOI: 10.1208/s12249-014-0100-4
33. Pescina S, Carra F, Padula C, Santi P, Nicoli S. Effect of pH and penetration enhancers on cysteamine stability and trans-corneal transport. Eur J Pharm Biopharm. 2016;107:171-179.
DOI: 10.1016/j.ejpb.2016.07.009
34. Santer V, Chen Y, Kalia YN. Controlled non-invasive iontophoretic delivery of triamcinolone acetonide amino acid ester prodrugs into the posterior segment of the eye. Eur J Pharm Biopharm. 2018;132:157-167.
DOI: 10.1016/j.ejpb.2018.09.020
35. Yin X, Lin X, Ren X, et al. Novel multi-targeted inhibitors suppress ocular neovascularization by regulating unique gene sets. Pharmacol Res. 2019;146.
DOI: 10.1016/j.phrs.2019.104277
36. Lima e Silva R, Kanan Y, Mirando AC, et al. Tyrosine kinase blocking collagen IV-derived peptide suppresses ocular neovascularization and vascular leakage. Sci Transl Med. 2017;9(373).
DOI: 10.1126/scitranslmed.aai8030
37. Patel SR, Berezovsky DE, McCarey BE, Zarnitsyn V, Edelhauser HF, Prausnitz MR. Targeted administration into the suprachoroidal space using a microneedle for drug delivery to the posterior segment of the eye. Investig Ophthalmol Vis Sci. 2012;53(8).
DOI: 10.1167/iovs.12-9872
38. Jung JH, Park S, Chae JJ, Prausnitz MR. Collagenase injection into the suprachoroidal space of the eye to expand drug delivery coverage and increase posterior drug targeting. Exp Eye Res. 2019;189.
DOI: 10.1016/j.exer.2019.107824
39. Nagaraj R, Bijukumar DR, Mathew B, Scott EA, Mathew MT. A review on recent advancements in ophthalmology devices: Currently in market and under clinical trials. J Drug Deliv Sci Technol. 2019;52:334-345.
DOI: 10.1016/j.jddst.2019.04.038
40. Baker-Schena L. Drug delivery for the posterior segmen the posterior segment. Eyenet Mag. 39-44.
41. Al-Halafi AM. Nanocarriers of nanotechnology in retinal diseases. Saudi J Ophthalmol. 2014;28(4).
DOI: 10.1016/j.sjopt.2014.02.009
42. Wang Y, Rajala A, Rajala R. Lipid nanoparticles for ocular gene delivery. J Funct Biomater. 2015;6(2).
DOI: 10.3390/jfb6020379
43. Kakkar S, Singh M, Mohan Karuppayil S, et al. Lipo-PEG nano-ocular formulation successfully encapsulates hydrophilic fluconazole and traverses corneal and non-corneal path to reach posterior eye segment. J Drug Target. 2021;29(6).
DOI: 10.1080/1061186X.2020.1871483
44. Arranz-Romera A, Esteban-Pérez S, Molina-Martínez IT, Bravo-Osuna I, Herrero-Vanrell R. Co-delivery of glial cell–derived neurotrophic factor (GDNF) and tauroursodeoxycholic acid (TUDCA) from PLGA microspheres: potential combination therapy for retinal diseases. Drug Deliv Transl Res. 2021;11(2).
DOI: 10.1007/s13346-021-00930-9
45. Wen Y, Jia H, Mo Z, et al. Cross-linked thermosensitive nanohydrogels for ocular drug delivery with a prolonged residence time and enhanced bioavailability. Mater Sci Eng C. 2021;119.
DOI: 10.1016/j.msec.2020.111445
46. Navarro-Partida J, Altamirano-Vallejo JC, Rosa AGD la, Armendariz-Borunda J, Castro-Castaneda CR, Santos A. Safety and tolerability of topical ophthalmic triamcinolone acetonide-loaded liposomes formulation and evaluation of its biologic activity in patients with diabetic

macular edema. Pharmaceutics. 2021; 13(3).
DOI: 10.3390/pharmaceutics13030322

47. Loftsson T, Stefánsson E. Aqueous eye drops containing drug/cyclodextrin nanoparticles deliver therapeutic drug concentrations to both anterior and posterior segment. Acta Ophthalmol; 2021.
DOI: 10.1111/aos.14861

48. Bhatt P, Fnu G, Bhatia D, Shahid A, Sutariya V. Nanodelivery of resveratrol-loaded PLGA nanoparticles for age-related macular degeneration. AAPS Pharm SciTech. 2020;21(8).
DOI: 10.1208/s12249-020-01836-4

49. Pinto J, Ahmad M, Guru BR. Enhancing the efficacy of fluocinolone acetonide by encapsulating with PLGA nanoparticles and conjugating with linear PEG polymer. J Biomater Sci Polym Ed. 2019;30(13).
DOI: 10.1080/09205063.2019.1625524

50. Nikita., Aqil M, Sultana Y. A grafted copolymer-based nanomicelles for topical ocular delivery of everolimus: Formulation, characterization, ex-vivo permeation, in-vitro ocular toxicity, and stability study. Eur J Pharm Sci. 2021;159.
DOI: 10.1016/j.ejps.2021.105735

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