Nanoparticulate Transscleral Ocular Drug Delivery

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Abstract

Ocular drug delivery is one of the most challenging areas of drug delivery due to the unique mostly avascular nature of the major eye structures and presence of two blood barriers. Effectiveness of a more conventional systemic delivery falls short due to low drug levels in the eye tissue. Periocular approaches require penetration of fibrous sclera and present their own limitations. Utilization of nanotechnology presents new avenue of drug system development with potential to penetrate protective barriers and sustain ample tissue saturation. More specifically, transscleral delivery permits a range of applications in targeted delivery, gene, stem cell, protein and peptides, oligonucleotide, and ribozyme therapies. The exciting range of current applications is expounded in this review.

Keywords: Ocular delivery; Transscleral delivery; Drug delivery systems; Nanotechnology; Nanoparticle; Drug delivery; Macular degeneration; Retina

Introduction

Ocular drug delivery has remained one of the most challenging tasks for pharmaceutical researchers. The unique and complex structure of the eye restricts the entry of drug molecules at the required site of action. The eye is anatomically divided into the anterior and posterior segments with the lens–iris barrier roughly demarcating the two segments. The anterior segment consists of the front one-third of the eye that mainly includes pupil, cornea, iris, ciliary body, aqueous humor, and lens while the posterior segment consists of the back two-thirds of the eye that includes vitreous humor, retina, choroid, macula, and optic nerve (Figure 1) [1,2]. Further, the anatomy of the eye presents a unique system with two barriers that prevents penetration of substances from the blood, namely, the blood-aqueous and blood-retinal barrier [3].

There are a large number of major diseases affecting the eye including Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), cataract, Proliferative Vitreoretinopathy (PVR), uveitis, Cytomegalovirus (CMV), and glaucoma. Table 1 highlights the classification, signs and symptoms and current treatment options for these diseases [4-38].

Ocular drug delivery methods to treat anterior segment disease include topical (i.e. eye drops, ointment), systemic, and periocular (i.e. subconjunctival injections, implants) administration routes.
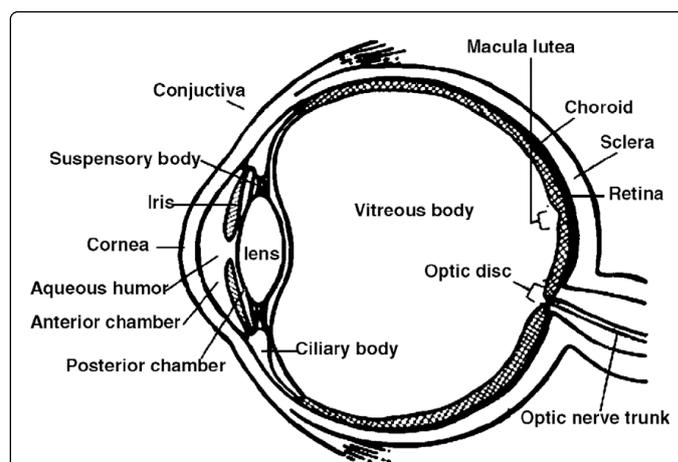

Figure 1: Schematic representation of major structure of the eye. The anterior segment includes pupil, cornea, iris, ciliary body, and aqueous humor. The lens separates anterior portion from posterior, which includes vitreous humor, retina, choroid, macular, and optic nerve. Sclera encasing the whole eye protects it impedes penetration of majority external agents. Reprinted with permission from reference [1]

Disease	Classification	Signs and symptoms	Treatment
AMD	Dry AMD (non-exudative)	Break down of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaries	Specific high dose formulation containing antioxidants, zinc and vitamin supplements

		Growth of abnormal blood vessels behind the retina, macula, disruption of Bruch's membrane and degeneration of RPE leading to complete loss of vision	Intravitreal injection of anti-VEGF agents like ranibizumab, pegaptanib sodium and bevacizumab [5-13].
	Wet AMD (Exudative)		
DME	Focal or non-cystoid DME	Small aberrations in retinal blood vessels followed by intra-retinal leakage	Focal or grid lasers and steroids [14-16].
	Diffuse or cystoids DME	Formation of microcrysts and dilation of retinal capillaries	
PVR	Based on the inflammation of retina: focal, diffuse, subretinal, circumferential, anterior displacement based on the location of scar tissue: anterior, posterior	Simple scar formation and proliferation of cells in vitreous and retina	Surgery and adjunctive treatment after surgery so as to avoid relapses (5-fluorouracil and low molecular weight heparin) [17-19].
Uveitis	Anterior uveitis, intermediate uveitis, posterior uveitis, pan-uveitic uveitis	Inflammation occurs in the middle layer of eye (uvea)	Corticosteroids and immunosuppressive agents [20-22].
CMV		Inflammation of the retina, retinal detachment and complete blindness	Cidofovir, ganciclovir (GCV) and foscarnet [22-24].
Glaucoma	Primary Open Angle Glaucoma (POAG) Angle Closure Glaucoma (ACG)	Obstruction to the outflow of aqueous humor from the anterior segment	Prostaglandin analogs, beta-adrenergic receptor antagonists, alpha2-adrenergic agonists parasympathomimetics, carbonic anhydrase inhibitors [25-29].
Conjunctivitis/red eye	Based on the structures: blepharoconjucntivitis, keratoconjucntivitis inflammation, and episcleritis	Infection of conjunctiva, redness, irritation, grittiness and watering of the eyes	Allergic infections are treated using anti-histaminics and non-steroid anti-inflammatory agents and bacterial conjunctivitis is treated using antibiotics and corticosteroids [30-33].
Cataract	Basis of etiology: age related, congenital, secondary, traumatic, basis of location of opacity: anterior cortical, anterior polar, anterior subcapsular, nuclear, posterior cortical, Posterior subcapsular	Lens opacities that obstruct the passage of light	Surgical treatment may either involve extracapsular surgery and photoemulsification [34-38].

Table 1: Major ocular diseases, signs and symptoms and current treatment

Table 2 provides a general overview of various delivery routes. Systemically administered drugs reach the retino-choroidal tissue via blood circulation; this is sufficient for many drugs to achieve therapeutic levels in the eye. However, because the outer and inner blood-retinal barriers limit influx of drug into the retina (and vitreous), lar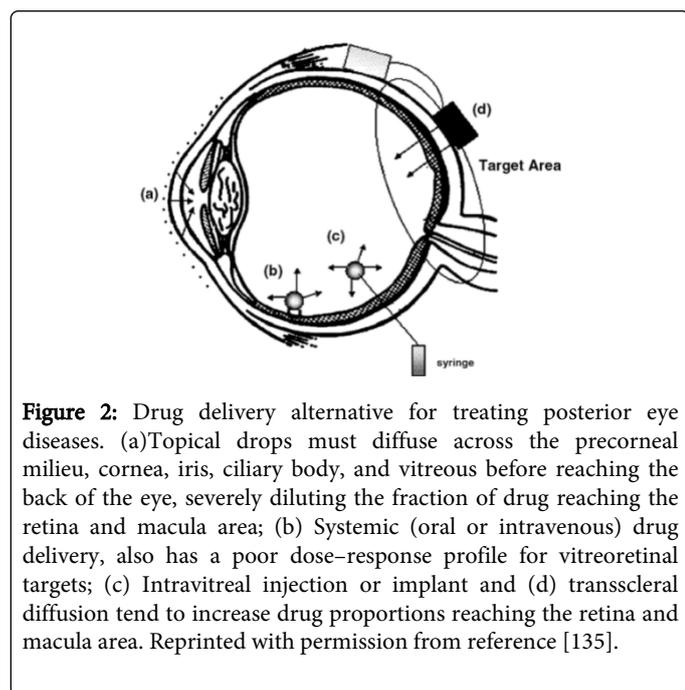ge doses of the drug are required in order to achieve and maintain therapeutic concentrations [4]. This usually leads to unwanted side effects, as the drug also accumulates in other tissues of the body. Periocular injections avoid the side effects associated with systemic delivery, but carry increased risks of retinal detachment, cataract formation, and other ocular maladies.

Route	Benefits	Challenges	Application in the treatment of diseases
Topical	High patient compliance, self-administrable and noninvasive	Higher tear dilution and turnover rate, cornea acts as barrier, efflux pumps, BA <5%	Keratitis, uveitis, conjunctivitis, scleritis, episcleritis, blepharitis
Oral/Systemic	Patient compliant and noninvasive route of administration	BAB, BRB, high doses causing toxicity, BA<2%	Scleritis, episcleritis, CMV retinitis, PU
Intravitreal	Direct delivery to vitreous and retina, sustains drug levels, evades BRB	Retinal detachment, hemorrhage, cataract, endophthalmitis, patient incompliance	AMD, PU, BRVO, CRVO, DME, CME, UME, CMV retinitis
Intracameral	Provides higher drug levels in the anterior chamber, eliminates usage of topical drops, reduces corneal and systemic side effects seen with topical steroid therapy	TASS, TECDS	Anesthesia, prevention of endophthalmitis, inflammation and pupil dilation

Subconjunctival	Delivery to anterior and posterior segment, site for depot formulations	Conjunctival and choroidal circulation	Glaucoma, CMV retinitis, AMD, PU
Subtenon	High vitreal drug levels, relatively noninvasive, fewer complications unlike intravitreal delivery	RPE, chemosis, subconjunctival hemorrhage	DME, AMD, RVO, uveitis
Retrobulbar	Administer high local doses of anesthetics, more effective than peribulbar, minimal influence on IOP	Retrobulbar hemorrhage, globe perforation, respiratory arrest	Anesthesia
Posterior juxtascleral	Safe for delivery of depot formulation, sustain drug levels up to 6 months to the macula, avoids risk of endophthalmitis and intraocular damage	Requires surgery and RPE acts as barrier	AMD

Table 2: Summary of routes of Administration, benefits and challenges in ocular delivery

Topical administration is the least invasive of the methods, and numerous topically applied drugs may enter the eye through the cornea, conjunctiva, and sclera [39,40]. However, only a small amount of a given drug penetrates the cornea, conjunctiva, and sclera to ultimately reach the target sites [41-43]. Some of the factors that affect this penetration of topically applied drugs include, but are not limited to, lachrymation, aqueous production, blood flow, and barriers imposed by the corneal epithelium and endothelium and by the stromal tissues of the cornea and sclera [43-45].

Figure 2: Drug delivery alternative for treating posterior eye diseases. (a)Topical drops must diffuse across the precorneal milieu, cornea, iris, ciliary body, and vitreous before reaching the back of the eye, severely diluting the fraction of drug reaching the retina and macula area; (b) Systemic (oral or intravenous) drug delivery, also has a poor dose–response profile for vitreoretinal targets; (c) Intravitreal injection or implant and (d) transscleral diffusion tend to increase drug proportions reaching the retina and macula area. Reprinted with permission from reference [135].
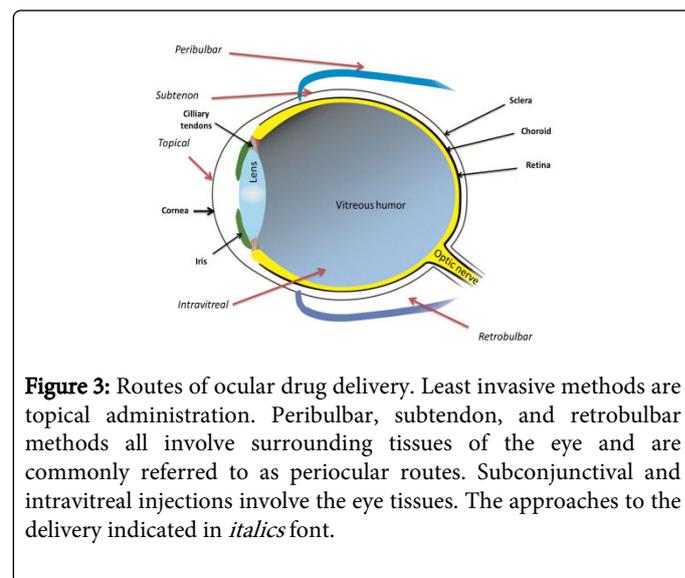
Consequently, topically applied drugs must be of relatively high concentration with frequent instillations, to achieve and/or maintain therapeutic concentrations, even for tissues in the anterior segment. In addition to the above mentioned factors, delivery of drugs to the posterior segment is even more challenging, due to the longer diffusion distance and the a cellular nature of the vitreous body. Thus, very often, methods alternative to topical administration are used to deliver drugs to the posterior vitreous, retina, or choroid (Figure 2).

Transscleral Drug Delivery Systems

Intravitreal injections have gained considerable momentum during the past two decades. This method involves injection of drug solution directly into vitreous via pars plana using a 30 G needle. Unlike other routes, intravitreal injection offers higher drug concentrations in vitreous and retina. Due to the uniqueness of the vitreous environment, the pharmacokinetics of the drug need to be considered to ensure adequate tissue drug levels and safe elimination, which is closely related to the molecular weight of the substance. Linear and globular shaped molecules (especially protein and peptide drugs) with molecular weight greater than 40 and 70 kDa respectively tend to cause longer retention in vitreous humor [46]. Though intravitreal administration offers high concentrations of drugs in retina, it is associated with various short term complications such as retinal detachment, endophthalmitis and intravitreal hemorrhages [47]. Moreover, patients need to be carefully monitored for specific time periods following intravitreal injections to ensure minimal procedure complications.

Periocular route has been considered as the most promising and efficient route for administering drugs to the posterior eye segment. Periocular refers to the region surrounding the eye and includes peribulbar, posterior juxtascleral, retrobulbar, subtenon and subconjunctival routes (Figure 3).

Figure 3: Routes of ocular drug delivery. Least invasive methods are topical administration. Peribulbar, subtendon, and retrobulbar methods all involve surrounding tissues of the eye and are commonly referred to as periocular routes. Subconjunctival and intravitreal injections involve the eye tissues. The approaches to the delivery indicated in *italics* font.

Drug solutions are placed in close proximity to the sclera which results in high retinal and vitreal concentrations, as the sclera is made up of fibrous tissue and offers less resistance to the permeation of Active Pharmacological Agents (APIs) [48].

Although intravitreal injections via the pars plana place the drug directly into the posterior segment, bypassing the corneo-scleral barriers, many of the vitreoretinal diseases (i.e. Age-Related Macular Degeneration (AMD) and diabetic retinopathy) for which intravitreal injections targeted are not controlled by a single injection, and the need for multiple injections increases the potential for cataract, retinal detachment, vitreous hemorrhage, and endophthalmitis. One of the alternative routes of drug delivery to the posterior segment is via the sclera. In humans, the sclera is relatively thick near the limbus, thin at the equator, and much thicker near the optic nerve. The total scleral area is 16-17 cm^2 [45,46,49,50]. Surgical thinning of the sclera demonstrates that scleral permeability is inversely proportional to the thickness [51]. Thus, the ideal location for transscleral drug delivery is near the equator at 12–17 mm posterior to the corneoscleral limbus. However, the thinness of the area would also make this site more susceptible to needle or instrument perforation.

Traditionally, subconjunctival, subtenon and retrobulbar injections have been used clinically to administer corticosteroids and local anesthetics, and it is known that higher concentrations in the posterior tissues can be achieved by these injections as opposed to topical eye drops [52,53]. Relatively high permeability of sclera to macromolecules has revived interest in this route of drug administration [50,51]. Delivery of macromolecules is important therapeutically, since anti-angiogenic antibodies, oligonucleotides, growth factors, and trans-gene expression products are all large molecules. Development of controlled release materials and dosage forms may provide means to achieve long duration of action and less frequent drug administration. This article gives an update on selected aspects of transscleral drug delivery. Particular emphasis is directed to the nanoparticulate systems of transscleral drug delivery for various ocular major diseases.

Periocular penetration routes

The periocular (transscleral) route of delivery is gaining increased interest as a promising alternative to the intravitreal administration for drug delivery to the choroid, retina, and vitreous [48]. In transscleral drug delivery to the posterior eye, the drug delivery system (e.g. solution or implant) is placed into the periocular space. Several possible sites are available, including subconjunctival, sub-tenon, peribulbar, posterior juxtascleral and retrobulbar spaces (Figure 4) [48].

It has been demonstrated that the transscleral route can deliver therapeutically effective drug levels for the treatment of choroidal neovascularization associated with age-related macular degeneration [54,55]. It has also been demonstrated that the periocular (transscleral) route can be used for delivery of large molecules to the choroid and the retina in vivo [56,57].

The drug may permeate from the periocular space into the vitreous (or another target tissue) via (1) anterior chamber, (2) systemic circulation or (3) direct penetration pathway. In the anterior chamber route, the drug diffuses into the aqueous humor either directly across the sclera and ciliary body or indirectly via the tear fluid and cornea after it has refluxed through the conjunctiva. Thereafter, the drug may permeate further to the posterior chamber and vitreous. In the systemic circulation route, the drug is absorbed into general circulation via conjunctival, episcleral, or choroidal vessels; then, it is diluted in the circulation, and later returned to the eye with blood flow.
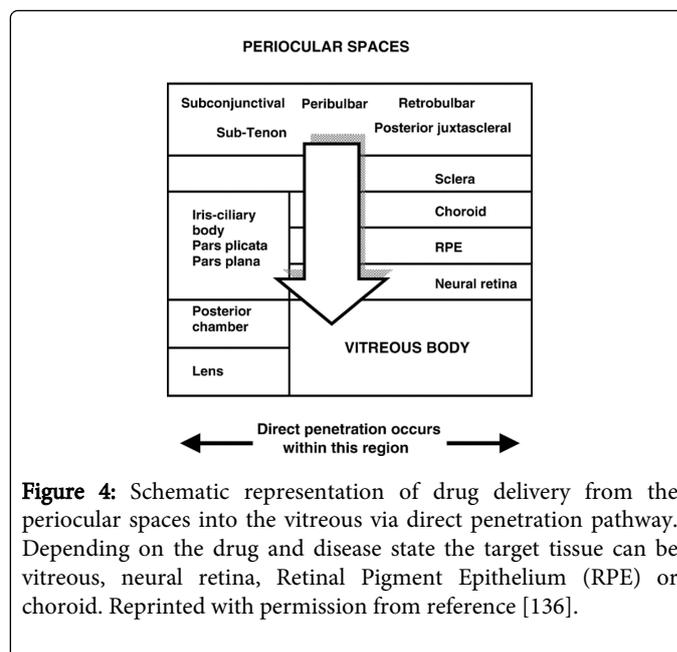

Figure 4: Schematic representation of drug delivery from the periocular spaces into the vitreous via direct penetration pathway. Depending on the drug and disease state the target tissue can be vitreous, neural retina, Retinal Pigment Epithelium (RPE) or choroid. Reprinted with permission from reference [136].

In the direct penetration pathway, the drug permeates into the vitreous through the underlying tissues. As seen in Figure 4, there is no single pathway after the drug has passed across the sclera. In the anterior eye, the drug may diffuse through the ciliary body (pars plicata or pars plana) into the posterior chamber and vitreous. In the posterior eye, the drug has to permeate across the choroid, Retinal Pigment Epithelium (RPE), and neural retina in order to reach the vitreous.

It is also important to consider that drug delivery across the sclera is governed in part by the transient diffusion of a solute across the tissue that typically occurs over a time course of minutes, unless some type of sustained-release formulation or device is used. Sustained drug delivery systems can provide sustained drug levels to a particular tissue thereby significantly reducing the dosing frequency and the associated complications. Several delivery systems including implants, scleral plugs, and micro-and nanoparticles have been used for this purpose [58-62]. Among these systems, the particulate systems offer several advantages including ease of repeated injections and biodegradability. In addition, nanoparticles have the advantage of cellular entry, which can be used in the delivery of macromolecules like DNA and proteins inside the cells [63]. The right combination of the drug/polymer can control the rate of delivery of a particular drug from these systems and extend the duration for which the drug is delivered.

Experimental studies aimed at determining scleral permeability typically derive scleral permeability for a particular solute from steady-state flux data. One must recognize that in the absence of some type of sustained-release system, drug–sclera contact times would be too brief to permit the attainment of steady-state flux. Consequently, the in vitro flux measurements would be expected to over-estimate transscleral drug delivery [64]. Sustained drug delivery to the retina by the periocular (transscleral) route would require that the delivery system be retained at the periocular site for a prolonged time so that the drug can be released from the device and become available to the retina. In the case of gene delivery, it would be ideal if the system penetrates the sclera and enters into the choroid and retina where the cells in the choroid or the retina can be transfected. Thus, based on

clinical need, the choice of a particulate delivery system can be made. The disposition of particles after periocular administration is size dependent. Specifically, particles in the range of 200–2000 nm were almost completely retained at the site of administration for at least two months while the smaller 20 nm particles were cleared rapidly from the site of administration.

Transscleral diffusion

A relatively newer method of drug delivery, transscleral delivery, is a less invasive method in which the drug permeates through ocular tissues to reach the neuroretina. Transscleral delivery includes avenues such as subconjunctival, retrobulbar, peribulbar, sub-Tenon's and intrascleral delivery [65]. An overview of these approaches and their applications are summarized in Table 3 [65,66].

Avenue of delivery	Mechanism of application	Risks and limitations	Common uses
Retrobulbar	Drug is injected between the inferior and lateral rectus muscles, and the needle is directed posteriorly until resistance from the orbital septum is met. The needle is then directed towards the apex until resistance from the intermuscular septum is met	Blood vessel laceration, globe perforation, orbital hemorrhage, diplopia, artery occlusion, and brainstem anesthesia	Preoperative analgesia, Postoperative analgesia, akinesia and control of intraocular Pressure
Peribulbar	This method can be further classified as circumocular, periocular, periconal and apical based on depth of needle penetration	Similar to retrobulbar delivery, but the risk of injury to intraorbital structures is milder	Preoperative analgesia, Postoperative analgesia, akinesia and control of Intraocular pressure
Subtenon's	Injection of drug into a fascial sheath of connective tissue between the conjunctiva and episcleral plexus	Difficult penetration of drugs through the sclera and choroid. Rapid drug removal by the choroidal circulation	Analgesia, local anesthesia, triamcinolone acetonide and antibiotics
Subconjunctival	Injection of drug beneath the conjunctiva, providing a localized and minimally invasive means of delivery to the posterior eye	Dependent on pharmacodynamics of drug and diffusion through sclera and choroid	Bioactive proteins, Prostaglandins and dexamethasone

Table 3: Overview of existing transscleral drug delivery techniques [65,66].

Barriers to Transscleral Drug Delivery

Although transscleral methods eliminate some of the side effects of intravitreal delivery, they in turn have their own limitations. Because the drug molecules must cross through several layers of tissue, the bioavailability of the drug at the target site can sometimes be drastically reduced and, thus, may require very high doses to be effective. These barriers are categorized into three major groups: static, dynamic and metabolic [66]. Table 4 provides a quick overview of these three barrier types [66]. Static barriers include the tissues that must be penetrated (e.g., sclera, Bruch's membrane-choroid and RPE).

Dynamic barriers include blood flow, lymphatic drainage, transport proteins of the RPE, drug efflux pumps, organic ion transporters and bulk fluid flow from intraocular drainage systems. Metabolic barriers include enzyme systems such as cytochrome P450 and lysosomal enzymes, which have the ability to degrade or detoxify drugs. Mathematical models of posterior segment drug delivery by subconjunctival injection reveal that the dominant pathway for entry into the vitreous is direct penetration, while recirculation or movement from the aqueous to vitreous chambers is not significant [67-70].

Static		Dynamic		Metabolic
Sclera	permeability decreases with increasing molecular radius and lipophilicity. Permeability increases with negatively charged solutes	Blood and lymphatic flow	high flow rates in conjunctiva and choroid may lead to faster drug elimination and minimal drug penetration	Cytochrome P450
Choroid and Bruch's membrane	permeability decreases with increasing molecular weight and lipophilicity. Permeability increases with negatively charged solute	Bulk fluid flow	convective flow may lead to decreased penetration of drugs	Lysosomal enzymes
RPE	permeability decreases with increasing molecular radius and increases with increasing lipophilicity	Proteins and channels	Transport proteins, drug efflux pumps and ion transporters	

Table 4: Barriers to transscleral drug delivery [66].

Conjuctiva is a thin and transperant membrane, having rich supply of capillaries and lymphatics (Figure 5), therefore drugs administered through conjuctival space need to be cleared through blood and lymph.

Due to loose junction barrier of conjuctival blood vessels, drug molecules can transport into blood circulation by pinocytosis and/or convective approach through paracellular pores in the vascular endothelial layer.
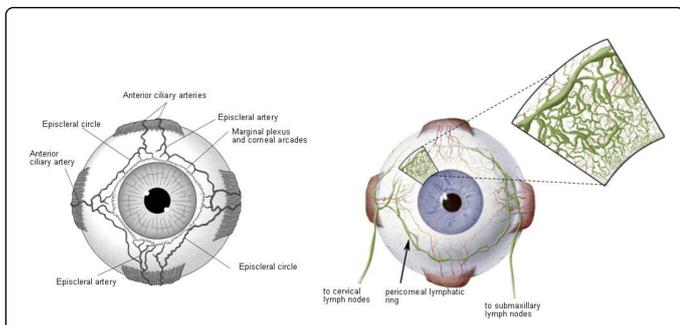
Figure 5: Schematic representations of subconjunctival or episcleral blood vessels, and lymphatics network. Schematic representations of subconjunctival or episcleral blood vessels, and lymphatics network. (Adapted from Robinson MR, Lee SS, Kim H, et al. A rabbit model for assessing the ocular barriers to the transscleral delivery of triamcinolone acetonide, Exp. Eye Res. 2006, 82, 479-487, with permission from Elsevier Inc., and The Human Eye with permission from Sinauer Associates, Inc., copyright 1999) [138].

Figure 6: Schematic of blood-retinal barrier, and capillary wall in the retina and the choroid. Reprinted with permission from reference [138].

The conjuctival lymphatics also act as an efflux system for the efficient elimination of drug. Therefore, drugs transported by lymphatics alongwith elimination by blood circulation can contribute to systemic circulation after filtered through lymphatic systems [71-74].

Sclera mainly consists of collagen fibers and proteoglycans embedded in an extracellular matrix. Permeability through scleral is strongly dependent on the molecular radius, as it decreases roughly exponentially with molecular radius. As mentioned earlier, surgical thinning of the sclera demonstrates that scleral permeability is inversely proportional to the thickness [51]. Thus, the ideal location for trans scleral drug delivery is near the equator at 12–17 mm posterior to the corneoscleral limbus. In addition to this, scleral permeability is also dependent on hydrophobicity of drugs. Hydrophilic drugs may diffuse through the aqueous medium of proteoglycans in the fiber matrix pores more easily than lipophilic drugs. Also, the charge of drug molecule affects the permeability. Positively charged compounds may exhibit poor permeability due to their binding to the negatively charged proteoglycan matrix [74].

Bruch's membrane-choroid is the highly vascularized tissues of the body to supply the blood to retina. Also the choroidal capillary endothelial cells are fenestrated and large in diameter (Figure 6).

In addition to this, histological studies have shown choroidal thickness changes from 200 μm at birth to about 80 μm by age 90 and chorioretinal diseases also affect choroidal thickness. In contrast, Bruch's membrane causes thickening with age. These changes cause calcification of elastic fibers, cross-linkzge of collage fibers and increased turnover of glycosaminoglycans. Thickness changes of choroid and BM might affect drug permeability from subconjunctiva or episcleral space into the retina and the vitreous [74].
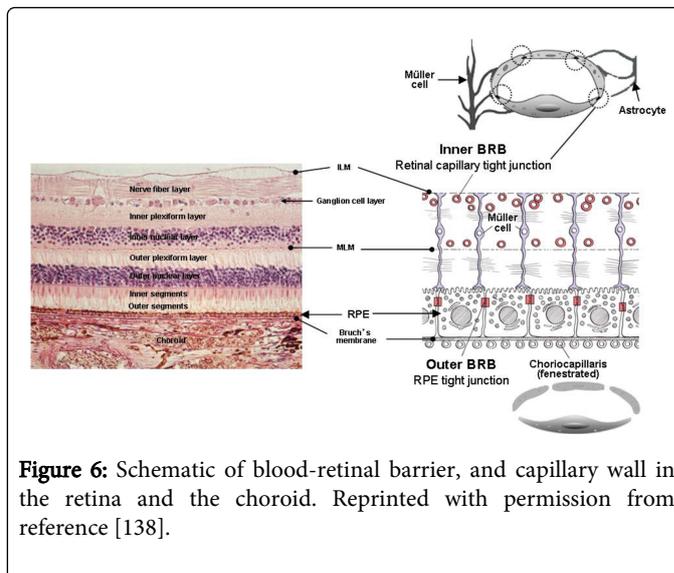
Blood-Retinal Barrier (BRB) is composed of tight junctions of retinal capillary endothelial cells and RPE, called iBRB for the inner and oBRB for the outer BRB, respectively, supported by muller cells and astrocytes. The function of BRB is to restrict drug transport from blood into retina. The muller cells and retinal capillary vessels are responsible to maintain the proper functioning of iBRB, in the uptake of nutrients and in the disposal of metabolites in the normal conditions. Dysfunction of Müller cells may contribute to a breakdown of the iBRB in many pathological conditions, such as diabetes. Astrocytes are known to increase the barrier properties of the retinal vascular endothelium by enhancing the expression of the tight junction and modifying endothelial morphology [74].

After systemic administration, drugs can easily enter into the choroid as choroid is highly vascularized tissue than retina. The choriocapillaris are fenestrated resulting in rapid equilibration of drug molecules will be achieved in the bloodstream with the extravascular space of the choroid. Therefore, oBRB (RPE) restricts further entry of drugs from the choroid into the retina. RPE is a monolayer of highly specialized hexagonal-shaped cells, located between the sensory retina and the choroid. The tight junctions of the RPE efficiently restrict intercellular permeation into the sensory retina.

In addition to the static, dynamic and metabolic barriers, other factors that must be considered in transscleral delivery include the individual pharmacokinetic properties of the drug. The pharmacokinetics of drug diffusion across these barriers is dependent on the molecular dimensions, molecular weight, atomic charge and chemical components of the drug. In vitro studies demonstrated that the human sclera is permeable to 70 kDa dextran [50]. The radius of the molecule is considered to be a more important predictor of permeability than the weight and charge [50]. Finally, the solubility of the drug compounds is impacted by the water and lipid interactions. Hydrophilic compounds tend to permeate through the sclera more rapidly than lipophilic (hydrophobic) molecules, making the delivery of lipid-dominant molecules such as corticosteroids via transscleral routes more challenging [51]. However, a balance may be critical since many lipophilic compounds can easily penetrate the RPE; problems such as toxicity can arise due to lack of drug elimination. The delivery of drugs via the transscleral route continues to undergo investigation owing to the potential benefits over systemic and intravitreal delivery.

Nanoparticulate Transscleral Drug Delivery Systems

Colloidal carriers have been widely exploited in the field of drug delivery science. It provides a more selective targeting along with sustained release of molecules at the desired site. Applications of nanotechnology can be very exciting in the treatment of a gamut of diseases affecting the anterior as well as the posterior segment of the eye. One has to understand the physiological and biochemical factors involved in normal and pathological conditions for designing a successful ocular drug delivery system. Delivery of a drug via nanotechnology-based product fulfills mainly three objectives as follows:

- Enhancement of drug permeation;
- Controlled release of the API; and
- Targeting of the delivery [71].

Colloidal systems consisting of micro/nanoparticles, micro/nanoemulsions, nanosuspensions, liposomes, dendrimers, niosomes, and cyclodextrins have also been exploited to achieve optimal drug delivery [46,58,59,61,63,71].

Many sustained intraocular drug delivery methods have been developed as alternatives to implantation. Ocular drug delivery systems using particulates have been developed, which provide sustained release with high target specificity in the form of microspheres and microcapsules with diameters of 1–1000 μm, as well as nanospheres and nanocapsules with diameters of less than 1 μm [75-76]. Drugs can be incorporated into biodegradable polymers to form either a matrix system or a reservoir system [62]. In a matrix system, the drugs and polymer are combined and the drug is released through diffusion from the polymer matrix with simultaneous polymer degradation. This system is used for micro- and nanospheres. The reservoir-type system involves encapsulating drugs within polymeric shells and the system is used for biodegradable micro- and nanocapsules [62]. Some of the commonly used synthetic biodegradable polymers are the aliphatic polyesters such as Polylactic Acid (PLA), Polyglycolic Acid (PGA), Poly (Lactic-Co-Glycolic Acid) (PLGA) and poly (caprolactone) [4,75,76]. These polymers are appropriate for controlled-release applications because they are nontoxic, nonimmunogenic and degrade through enzymatic reactions and hydrolysis to natural metabolic products over a period of months to years [77-78]. Drug-release profiles can be modified through variations in polymer molecular weights and copolymer formulations [76]. An emulsion–diffusion process is used to encapsulate drugs in micro- and nanocapsules, while solvent evaporation is used to prepare micro- and nanospheres using an oil-in-water emulsion for hydrophobic drugs or an oil-in-oil emulsion for improved encapsulation efficiency for hydrophilic drugs [62,79-81]. The particulates are suspended in a carrier solution to enable ocular injection. Intravitreal injections can potentially impair vision due to clouding. However, microspheres larger than 2 μm tend to settle out owing to gravity, whereas nanoparticulates diffuse quickly and localize within ocular tissues [82]. Table 5 summarizes major research contributions in the area of nanoparticle-transscleral delivery [80,81,85-90,92,101,82-107,109-111].

Category	Approach	Research Outcome
Biodegradable Microspheres	Targeting drugs to retinal pigment epithelial (RPE) cells with the use of surface modified microspheres of poly (lactic acid)	They studied the possibility of targeting drugs to retinal pigment epithelial (RPE) cells with the use of surface-modified microspheres. A fluorescent dye, 1,4-bis[2-(5-phenyloxazolyl)]-benzene (POPOP), was incorporated into microspheres of poly(lactic acid) for use as a marker to evaluate drug delivery. Phagocytosis of the microspheres, with or without gelatin precoating, was carried out at $37^\circ C$ and $4^\circ C$. In comparison with bare microspheres, gelatin precoating significantly enhanced phagocytosis (P<0.001) at the same incubation times. These results suggested that drug delivery to RPE cells may be feasible by means of surface-modified polymer microspheres [83].
	L-lactic acid, and DL-lactic acid with different molecular weights or the copolymers of different monomer compositions	Investigated phagocytosis of biodegradable microspheres containing a drug by retinal pigment epithelial (RPE) cells and drug release within the cells to evaluate the potential usefulness of microspheres for intracellular drug delivery. The microspheres containing a non-bioactive fluorescent dye (rhodamine 6GX) as a model drug were prepared by a solvent evaporation method. The dye was released with time from every microsphere and the release was controlled by changing the type of polymers constituting microspheres. The microspheres containing the dye were phagocytosed by RPE cells and the dye was released intracellularly with time [84].
	Lyophilized RNA aptamer EYE001, PLGA Rasomer 502 H, chloroform, methylene chloride	Data showing the feasibility of delivering the anti-VEGF aptamer EYE001 in a sustained and controlled manner and in a biologically active form. The development of such an approach to drug delivery accompanies the advent of many potential antiangiogenic drugs for the treatment of various vision-threatening diseases that affect the posterior segment of the eye. Validation of this study would require testing the system in an in vivo model that would also address other various important questions [85].
Biodegradable Nano- & Microspheres of antiviral drugs	Ganciclovir	Effectiveness of ganciclovir-loaded 50:50 poly(D,L-lactide-co-glycolide) microspheres in 2% hydroxypropylmethylcellulose in inhibition of cytomegalovirus was tested in rabbits. Drug-loaded microspheres successfully minimized disruption of the retina, viritis, retinitis, and optic nerve degeneration [86].
Microsphere for (choroidal neovascularization)	PKC412 (Protein Kinase C inhibitor); PLGA (poly d,l – lectide co-glycolide)	Periocular injection of microspheres containing PKC412 caused significant suppression of the development of CNV at rupture sites in Bruch's membrane in pigs. Ten days after injection of microspheres containing 50% PKC412,

		PKC412 was detectable in the choroid, but not the retina or vitreous. Twenty days after injection of 25% PKC412 microspheres, levels of PKC412 in choroid, vitreous, and retina were lower than those after injection of 50% PKC412 microspheres, but still well above the level of detection. This suggests that the microspheres were providing sustained delivery of PKC412, with levels increasing between 10 and 20 days after injection and were able to suppress the development of CNV [87].
Microspheres and minitablets	Biodegradable polylactide (PLA), Triamcinolone acetomide (TA), Single or double emulsification solvent evaporation method	The double emulsification method and increasing drug input led to an increase in drug loading and encapsulation. TA could slowly cross the sclera tissue in vitro, with approximately 21% of the drug loaded in the donor compartment being diffused through the sclera in 45 days. The PLA-TA microspheres and mini-tablets appear promising for the controlled transscleral delivery of TA [88].
Biodegradable microparticles	Starch acetates are novel biodegradable polymers which undergo slower degradation and swelling than native starch.	Calcein-containing starch acetate microparticles were prepared by a modified water-in-oil-in-water double-emulsion technique. The cellular uptake of the starch acetate microparticles was analyzed using flow cytometry and confocal microscopy. The starch acetate microparticles are taken up by the RPE cells and the polymer can be degraded by the enzymes in these cells. Starch acetate microparticles may be suitable for drug delivery to the RPE [89].
Microparticle	Celecoxib; poly (D-L lectyde-coglycolyde); modified solvent evaporation technique;	This study demonstrated that a microparticulate system of celecoxib can be used periocularly for therapy in early background diabetic retinopathy. Potentially, such particulate systems can be used for the therapy of other disorders of the posterior segment. A sustained drug delivery system of celecoxib, in vivo, has beneficial effects in a rat model of early background diabetic retinopathy without any overt toxicity. Celecoxib microparticles may have potential as a locally administered preventive measure to delay the development or progression of the early pathophysiological changes in the retina as a result of diabetes [90].
Polymeric microparticles / nanoparticles	Poly-l-lactide (PLA), Triamcinolone acetomide (TA), o/w emulsion-solvent evaporation method	Single periocular injection of polymeric microparticles but not nanoparticles sustained effective levels of TA in choroid-RPE and retina for 2 months; with the TA delivery being greater in Choroidal neovascularization (CNV) induced rats than the control rats [91].
Steroidal nano- and microparticle	PLA nano- and microparticles, Budesonide, solvent evaporation technique, vascular endothelial growth factor (VEGF)	Budesonide is capable of inhibiting VEGF expression through glucocorticoid receptor activity. Subconjunctivally administered budesonide-PLA nano- and microparticles sustain retinal drug delivery [92].
Silicone Microneedles	Isotropic RIE technique with SF6/02 as etchant for microneedle fabrication. Solid out-of-plane Si microneedles was fabricated with needle heights ranging from 450 μm to 700 μm, and base widths ranging from 10 μm to 15 μm.	The results indicate that the microneedles should be able to penetrate soft ocular tissue and be able to deliver drugs successfully through the selected drug delivery route. The data obtained from the analysis indicated that the fabricated needles should be able to withstand the pressure exerted by a thin layer of fibrous human tissue. This process is minimally invasive, more effective than oral/topical administration of drugs and facilitates controlled delivery through the selected route [93].
Nanoparticle	Carboxylate-modified polystyrene FluoSpheres®	Periocular circulation (blood and lymphatic) plays an important role in the clearance of the 20 nm particles. The higher particle levels in the ocular tissues in the post-mortem studies indicate a dynamic physiologic barrier to the entry of particles into the ocular tissues after periocular administration. The particle size of the delivery system can play an important role in the observed retinal drug levels after periocular administration. Slow release nanoparticles with low clearance by blood and lymphatic circulations are suitable for prolonged transscleral drug delivery to the back of the eye [94].
	PLA (polylactide) nanoparticles (NPs), rhodamine 6G, Nile Red,	Intravitreous injection of PLA NPs appears to result in transretinal movement, with a preferential localization in the RPE cells. Encapsulated Rh diffuses from the NPs and stains the neuroretina and the RPE cells. The findings support the idea that specific targeting of these tissues is feasible. Furthermore, the presence of the NPs within the RPE cells 4months after a single injection shows that a steady and continuous delivery of drugs can be achieved. [72]
Cyclodextrin / polymeric nanoparticle	Diclofenac; Flurbiprofen; cyclodextrins; poly (D-L lectic-coglycolic) acid; poly-e-caprolacton	The formation of NSAIDs with cyclodextrins has been as an effective procedure to increase remarkably the bioavailability of the anti-inflammatory drugs. The efficiency of polymeric nanoparticles of polylacticpolyglycolic acid and the poly-ε-caprolactone as intraocular targeting of NSAIDs has also been proved, being the latter polymer more effective to increase the corneal permeation of the assayed drug flurbiprofen [95].
Cyclodextrin / Microparticles in eye drop suspension	Dexamethasone; Gamma Cyclodextrin;	A non-invasive method to deliver steroids in therapeutic levels to the retina in rabbits. Dexamethasone was formulated as somewhat water-soluble

		dexamethasone / gamma-cyclodextrin (gammaCD) microparticles in a low-viscosity aqueous eye drop suspension. The aqueous dexamethasone / gamma CD eye drop formulation was chemically stable during 7 months storage and well tolerated with no visible short-term side effects [96].
Biodegradable polymeric nanoparticle	Dexamethasone (DXM); poly(D,L-lactide-co-glycolide) PLGA nanoparticle; solvent evaporation process	The paper concerns both the optimization of DXM entrapment and its release from biodegradable PLGA nanoparticles prepared by the solvent evaporation process. Neither the evaporation rate of the organic solvent, nor the aqueous phase saturation with salt or the incorporation of lipid modified the encapsulation efficiency. The results demonstrate the feasibility of encapsulating dexamethasone and its subsequent delivery [97].
Trojan particles – Hybrid vector of nanoparticles with microparticles	Dexamethasone acetate (DXA); poly(D,L-lactide-co-glycolide) PLGA nanoparticle; 1,2-Dipalmitoyl-sn-Glycero-3-Phosphocholine (DPPC), hyaluronic acid (HA) Spray drying technique;	The presence of crystalline drug along with the nanoparticles considerably reduces the ability to load the polymeric matrix. These nanoparticles have been easily formulated into Trojan particles using DPPC and HA as excipients. The in situ release of drug loaded nanoparticles should favor their internalization within retinal pigment epithelial cells and might therefore increase the drug efficacy. This novel delivery system deserves to be evaluated in vivo to ascertain its interest for treating retinal affections [98].
Nanoparticle for cancer	Vinblastine; doxorubicin; poly (D-L lectic-coglycolic) acid;	This study suggests both vinblastine and doxorubicin are able to diffuse across human sclera. In addition, PLGA nanoparticles delivered doxorubicin at a slower rate across the sclera, and the liposome preparation resulted in the slowest delivery of drug [99].
Nanoparticle for gene delivery	Human serum albumin – nanoparticles (HSA-NP), desolvation technique, fluorescence labeled nanoparticle	Investigated the movement of intravitreally injected HSA-NP depended on both nanoparticle surface charge and retinal injury. The Müller cells might play an important role in the retinal penetration of nanoparticles. The anionic HSA-NP is a promising drug or gene delivery carrier to the sub-retinal space and RPE [100].
Nanostructured lipid carriers	Triamcinolone acetonide (TA); Triamcinolone acetonide Nanostructured lipid carriers (TA-NLC); high pressure homogenization	Nanostructured Lipid Carriers (NLC) have been developed for sustained release of Triamcinolone Acetonide (TA), a corticosteroid commonly indicated for macular oedema, neovascularization and other ocular inflammatory conditions. Drug release from NLC followed one-order kinetics. Ex vivo permeability studies confirmed that TA is able to diffuse through rabbit sclera in a sustained profile, following a zero-order kinetic model. Strong tissue binding was observed, providing a drug depot [101].
Nanoparticle Iontophoresis	PKC412 (Midostaurin), poly(d,l-lactide-co-glycolide) (PLGA 85:15, MW 12 kDa), oil-in-water emulsification-solvent diffusion evaporation Method.	Particles were characterized by a mean diameter of 194 nm, a zeta potential of (+) 74 mV, and drug loading of 21.5%. Result of anodal iontophoresis of nanoparticles resulted in transscleral delivery of 3.3±1.7 mcg and 3.6±0.6 mcg of PKC412 to rabbit ocular tissues. Combination of nanoencapsulation and iontophoresis may provide an opportunity for development of a practical non-invasive ocular delivery system [102].
Nanomolecule	Carboplatin, nanoparticulate carrier, co-acervation method, biodegradable and biocompatible protein (BSA),	Nanoparticulate-bound carboplatin has greater transscleral transport than commercially available carboplatin, especially in the first week after injection and may help enhance the proven adjuvant efficacy of periocular carboplatin over and above systemic chemotherapy in treating human retinoblastoma, especially those with vitreal seeds [103].
Nano and microspheres	Bevacizumab (Avastin®), PLGA [poly(DL-lactide-co-glycolide)] and PELGA [poly (ethylene glycol)-b-poly (D,L-lactic acid)], Age-related macular degeneration (AMD)	Bevacizumab can be released from nano- and microparticles of PLGA and PEGLA in a sustained fashion for over 91 days. The release rate could be adjusted by altering the drug/polymer ratio. However, bevacizumab activity still needs to be tested in vivo using animal models. Nevertheless, these results may offer improvements for the treatment of wet AMD using bevacizumab and may also improve cancer treatment using the same carriers for sustained release of the drug [104].
Polystyrene nanospheres	Polystyrene nanospheres, fluorescein derivative.	They injected nanospheres containing a fluorescein derivative into the vitreous cavity of pigmented rabbit eyes and evaluated their intraocular kinetics as drug carriers in vivo. Histological studies using a fluorescence microscope revealed that nanospheres with a diameter of 2 microm were seen in the vitreous cavity and trabecular meshwork, while nanospheres with a diameter of smaller than 200 nm were also observed in the retina as well as these tissues. These findings indicated that nanospheres may be beneficial as a drug carrier to the retina, vitreous and trabecular meshwork [105].
Neutral Proteases	Matrix metalloproteinase (MMP), macromolecules, molecular vectors	The present findings showed that there are several ways to facilitate drug delivery to the posterior retina in patient eyes. First, subconjunctival injections of MMPs could be made either before or with macromolecular therapeutics. Alternatively, molecular vectors might be used to enhance endogenous local production of MMPs. It also may be useful for enhancing the long-term

		delivery of macromolecules for the treatment of primary open-angle glaucoma, diabetic retinopathy, or agerelated macular degeneration [106].
Macromolecules; transscleral iontophoresis and intravitreal injection	Galbumin™ (gd-labeled albumin); a bovine albumin conjugated with gadolinium (Gd)	The distribution of a globular macromolecule in the eye was studied after transscleral iontophoresis and intravitreal injection. Transscleral iontophoresis primarily delivered macromolecule to the conjunctiva and nearby tissues under the site of the iontophoresis application. No Galbumin™ was detected in the anterior chamber or vitreous after iontophoresis. At 12 h after iontophoresis, a significant amount of Galbumin™ was cleared from the tissues. In the intravitreal injection study, the distribution of Galbumin™ in the vitreous humor was fast with a diffusion coefficient estimated to be close to that of free aqueous diffusion [107].

Table 5: List of research done on Nanoparticulate Transscleral Drug Delivery System

Applications of Nanoparticulate Transscleral Drug Delivery System

Nanotechnology for advanced drug delivery: The era of molecular medicine, which has been accelerated by the human genome project, has led to early disease detection through diagnostics and targeted drug and gene therapy. With the development of nanoparticles, barriers to drug delivery may be overcome at the organ, tissue, cellular, and subcellular levels. Nanoparticle drug delivery may be accomplished through gold nanospheres and rods, nanowires, nanotriangles, nanostars, nanocubes, and nanorice. The size of these nano configurations varies from 1 to 100 nm. Nanoplatforms include organic nanostructures, polymeric nanoparticles, lipid systems-liposomes, self-assembling micelles, dendrimers, and carbon nanostructures (e.g. nanotubes). Inorganic nanostructures include metal nanoparticles and nanoshells, silicon nanostructures, nanocrystals, and quantum dots. Hybrid nanostructures, combining two to three of those previous listed can also be produced.

Tumor cell targeted drug delivery: Studies were described in which polymeric nanoparticles were used for tumor-targeted delivery to block tumor blood vessels and to mediate in vitro drug delivery of tamoxifen and paclitaxel in human cancer xenograph models [108-110].

Gene therapy: Nanoparticles present the potential to be used in the future for gene therapy, as a safer and more effective alternative to viral vectors to deliver full genes or gene-suppression agents to the eye. For example, gelatin based engineered nanoparticles have been used for gene delivery [111]. Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, which are second only to cataract as the leading cause of vision loss [112]. Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications [113]. Topical delivery to the eye is the most expedient way of ocular gene delivery. However, the challenge of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration [112]. Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transduce nondividing cells, leading to restriction of their clinical use [113]. The advanced delivery systems that prolong the contact time of the vector with the surface of the eye may enhance transgene expression, thereby facilitating non-invasive administration [112].

Multifunctional nanoemulsions for oral and intravenous delivery: Gadolinium-loaded nanoemulsion has been utilized for brain imaging in animal studies [114-133,134]. This imaging technology could be utilized for imaging within the eye to observe the results of various drug delivery modalities. In addition, gold nanostructures have been developed for OCT imaging along with superparamagnetics from oxide-gold-core–shelled nanoparticles (60 nm iron oxide nanoparticles with 5 nm gold shells) for MRI imaging.

Stem cell Therapy: Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina [111,135-137]. Current strategy for management of ocular conditions consists of eliminating the injurious agent or attempting to minimize its effects. The most successful ocular application has been the use of limbal stem cells, transplanted from a source other than the patient for the renewal of corneal epithelium. The sources of limbal cells include donors, autografts, cadaver eyes, and recently, cells grown in culture. Stem-cell Therapy has demonstrated great success for certain maladies of the anterior and posterior segment [115].

Protein and Peptide therapy: Delivery of therapeutic proteins/peptides has received a great attention over the last few years [116]. The intravitreous injection of ranibizumab is one such example. In order to develop design of optimized methods for sustained delivery of proteins and prediction of clinical effects of new compounds administered in the eye, basic knowledge of proteins and peptides is required [56]. However, several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery. A number of approaches have been used to overcome these limitations. Poor membrane permeability of hydrophilic peptides may be improved by structurally modifying the compound, thus increasing their membrane permeability. Ocular route is not preferred route for systemic delivery of such large molecules. Immunoglobulin G has been effectively delivered to retina by transscleral route with insignificant systemic absorption [56].

Oligonucleotide therapy: Oligonucleotide (ON) therapy is based on the principle of blocking the synthesis of cellular proteins by interfering with either the transcription of DNA to mRNA or the translation of mRNA to proteins. Among several mechanisms by which antisense molecules disrupt gene expression and inhibit protein synthesis, the ribonuclease H mechanisms are the most important. A number of factors have been determined to contribute to the efficacy of antisense ON. One primary consideration is the length of the ON species. Lengths of 17– 25 bases have been shown to be optimal, as longer ONs have the potential to partially hybridize with nontarget RNA species. Biological stability is the major barrier to consider when delivering both DNA and RNA oligonucleotides to cells. Protection

from nuclease action has been achieved by modification of phosphate backbones, sugar moiety, and bases [117].

Scleral Plug therapy: Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used, their molecular weights, and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy [60].

Ribozyme therapy: RNA enzymes or ribozymes are a relatively new class of single-stranded RNA molecules capable of assuming three-dimensional conformations and exhibiting catalytic activity that induces site-specific cleavage, ligation, and polymerization of nucleotides involving RNA or DNA. They function by binding to the target RNA moiety through Watson-Crick base pairing and inactivate it by cleaving the phosphodiester backbone at a specific cutting site. Successful implementation of this principle has been demonstrated in the work of Lewin and Hauswirth in the delivery of ribozymes in Autosomal dominated retinitis pigmentosa (ADRP). ADRP is caused by mutations in genes that produce mutated proteins and lead to the apoptotic death of photoreceptor cells [117]. The results of this study in rats may pave the way for ribozyme therapy in many other autosomal dominant eye diseases, including glaucoma.

Aptamer: Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets. They are isolated from complex libraries of synthetic nucleic acid by an iterative process of adsorption, recovery, and reamplification. They bind with the target molecules at a very low level with high specificity. One of the earliest aptamers studied structurally was the 15-mer DNA aptamer against thrombin, d(GGTTGGTGTGGTTGG) [118]. For ocular neovascularization and vascular permeability, Pegaptanib sodium is an RNA aptamer available from Eyetech Pharaceuticals/Pfizer to target VEGFb165 [117].

Transscleral Iontophoresis: Iontophoresis is a noninvasive technique in which a weak electric current is used to drive the penetration of charged molecules into and across percutaneous tissue. Iontophoresis has been used in several areas of medicine, and iontophoresis via the cornea has been in use in ophthalmologic practice and research for many years. However, with the development of potent drugs that can be applied topically, corneal iontophoresis is rarely used today. Maurice and Barza et al. performed transscleral iontophoresis by placing the iontophoretic probe over the pars plana and were able to deliver high concentrations of drugs to the vitreous humor. Placing the iontophoretic probe over the pars plana enabled them to bypass the lens–iris barrier, which prevented significant levels of drug from moving from the anterior to the posterior segment. These early studies on the use of iontophoresis for ocular drug delivery were conducted with devices that were clumsy or inconvenient; as the charged drug reservoir in solution had to be placed over the iontophoretic site. Transscleral iontophoresis therapy is a promising field, although at present, the full potential for its use in ophthalmology has not been realized.

Conclusion

Effective treatment of ocular diseases is a formidable challenge for scientists in the field especially because of the nature of diseases and presence of the ocular barriers especially in posterior ocular segments. An ideal therapy should maintain effective levels of drug for the longer duration following a single application. Drug delivery by topical and intravitreal routes cannot be considered safe, effective and patient friendly. Drug delivery by periocular route can potentially overcome many of these limitations and also can provide sustained drug levels in ocular pathologies affecting both segments. Transporter targeted delivery can be a promising strategy for many drug molecules. Nanoparticulate systems can substantially improve the current therapy and may emerge as an alternative following their periocular administration. In recent years, scientists have focused on designing a strategy with a multidisciplinary approach e.g. microneedle, microemulsion, nanosuspension, iontophoresis and MRI. Also, continued innovation in gene delivery appears to be very exciting for a gamut of diseases. Development of noninvasive delivery techniques will revolutionize ocular drug delivery. The potential for the growth of sustained drug delivery systems involving polymeric systems is limitless, and newer polymers would serve the purpose of controlled and sustained delivery for treating vision-threatening diseases. Advances in nanotechnology and noninvasive drug delivery techniques will remain in the forefront of new and novel ophthalmic drug delivery systems.

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