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DRUG TARGETING IN POSTERIOR SEGMENT OF EYE

Sourindra Narayan Deb*[1] and Suvakanta Dash[2]

[1]Department of Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Science, Guwahati, India.
[2]Principal, Girijananda Chowdhury Institute of Pharmaceutical Science, Guwahati, India.

***Corresponding Author: Sourindra Narayan Deb**
Department of Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Science, Guwahati, India.

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ABSTRACT

The presence of ocular barrier and anatomy and physiology of the posterior segment of eye limited the targeting of drug in diseases like age-related macular degeneration, cytomegalovirus retinitis, diabetic retinopathy, posterior uveitis and retinitis pigmentosa. Design of suitable drug dosage regimen can overcome these limitation of drug targeting. In this context the present review article focus on the development of different methods that will increase the efficacy of drug application, resulting in more successful therapy for patients with posterior segment of eye diseases. This article summarizes recent advances in the research and development of drug delivery methods of the posterior chamber of the eye, with an emphasis on the use of implantable devices as well as nanotechnology drug delivery system.

KEYWORDS: Posterior segment, Intravitral injection, Ocular implants, Thermoresponsive gels, Nanotechnology.

INTRODUCTION

The eye is an unique and very sensitive organ, both anatomically and physiologically as it contain several widely varied and complex structures with independent physiological functions. This provides the organ protection that doesn't allow entrance or passage of foreign substances. Due to this complexity of the eye many challenges has to face by the pharmaceutical scientist for drug delivery. Bioavailability of ocular drug depends upon some physiological properties and physiological factors. The different factors, that affect a drug's ocular bioavailability includes physiologic factors like protein binding,drug metabolism and lacrimal drainage, similarly the physicochemical characteristics of the drug substance, and product formulation are important factors influence the drug bioavailability. Drugs which are highly water-soluble, do not readily permeate the cornea. Ophthalmic suspensions, ophthalmic ointments mix faster than opthalmic solutions with lacrimal fluids, and can remain in the cul-de-sac for longer period of time, enhancing the bioavailability of the drug substance.[1]

Depending on the method of application, the drugs are distributed locally, regionally or systemically and may lead to various undesired side effects such as drug accumulation and toxicity. An exciting challenge for developing suitable drug delivery systems targeted for ocular diseases is one of the major focus of pharmaceutical scientists. There are several new ophthalmic drug delivery systems under investigation such as: hydrogels, nanoparticles, liposomes, ocular inserts/implants, dendrimers and transcorneal iontophoresis act to target in the corneal surface of the eye. Polymeric nanoparticles are also able to target diseases in the posterior segment of the eye such as age-related macular degeneration, cytomegalovirus retinitis, diabetic retinopathy,posterior uveitis and retinitis pigmentosa While the topical and systemic forms of drug delivery are useful in certain diseases.[2]

The treatment of these diseases requires a direct and local application of the agent to the posterior eye segment at a therapeutic concentration because the delivery of exogenous molecules to the intraocular tissues including the retina is significantly limited.[3]

This review will enlight the update, recent progress and trends in method of targeting of drug in posterior segment of eye.

Posterior Segment of Eye

Posterior segment refers everything behind the lens of the eye. This is the back two third of the eye that includes the anterior hyaloid membrane and all of the optical structures behind it. The vitreous humour, retina, choroid and optic nerve. Vitreous body is jelly like substance that fills the interior of the eye ball behind the

lens. The posterior segment of eye is affected by various vision threatening diseases. Diseases affecting posterior segment includes age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.[4] The most challenging task faced by today's scientist is formulating a suitable dosage form for ocular delivery. Delivery of drugs to the targeted ocular tissues is restricted by various precorneal, dynamic and static ocular barriers. In addition, therapeutic drug levels are not maintained for longer duration in target tissues.

For posterior ocular delivery, research has been immensely focused towards development of drug releasing devices and nanoformulations for treating chronic vitreoretinal diseases. These novel devices and/or formulations may help to surpass ocular barriers and associated side effects with conventional topical drops. Also, these novel devices and/or formulations are easy to formulate, no/negligibly irritating, possess high precorneal residence time, sustain the drug release, and enhance ocular bioavailability of therapeutics. An update of current research advancement in ocular drug delivery necessitates and helps drug delivery scientists to modulate their think process and develop novel and safe drug delivery strategies. Current review intends to summarize the existing conventional formulations for ocular delivery and their advancements followed by current nanotechnology based formulation developments. Also, recent developments with other ocular drug delivery strategies employing *in situ* gels, implants have been reviewed in details.[5]

Drug delivery to ocular tissues is delayed or prevented due to the presence of ocular barriers which makes drug delivery more difficult and challenging to deliver drug back of the eye (retina-choroid). To modulate and improve ocular drug delivery, it is important to overcome these ocular barriers.

Posterior Segment Barrier

Drug permeation to posterior ocular tissues is impeded by the presence of static (sclera, retinal pigment epithelium and blood capillary endothelial cells) and dynamic barriers (choroidal blood and lymph circulation). In addition, expression of efflux pumps on the cell membrane acts as a significant permeation barrier limiting the passage of drugs.

Sclera is the white part of the globe which is continuous with cornea and extends from limbus to the posterior segment of the eye. It is mostly composed of collagen fibers and mucopolysaccharides with poorly developed vasculature.[6,7] Thickness of sclera differs from anterior to posterior region. It is thick near the limbus and gradually decreases at the equator. Towards the posterior end, at optic nerve, sclera is almost double in thickness relative to anterior thickness. It offers higher permeability than cornea but relatively lesser than conjunctiva. Scleral permeability is strongly dependent on molecular radius, physicochemical properties and surface charge of the permeating molecule. Drug permeability gradually recedes with increasing molecular radius and hydrophobicity, thus limiting the rate of permeability through aqueous scleral pores.[8-10] Also, the opposite surface charge of drug molecules may restrict drug permeability due to charge interactions with negatively charged proteoglycans matrix. Choroid is sandwiched between sclera and Bruch's membrane.[11]

Choroid is a highly vascularized and fenestrated tissue supplying blood to inner retina. Thickness of choroid is an interesting fact, in a new born is 200 μm which gradually reduces with age. Not only age, but other disease. Factors also affect the choroidal thickness such as age related macular degeneration (AMD), choroidal atrophy, and high myopia.[12,13] At and above age 90, the choroidal thickness reduces below the half (80 μm) of the initial original thickness (200 μm).[14]

Bruch's membrane lies below the choroid and above the retinal epithelial cell membrane. It is a thick basement membrane produced by collaboration of choriocapillaries and Retinal Pigment Epithilium. The Changes in thickness of Bruch's membrane occurs in opposite direction to choroid with age i.e., thickness increases with age.[15] The causes of Variation in thickness results calcification of elastic fiber: higher collagen fiber cross-linking and glycosaminoglycan turnover.[16–18] Changes in the choroid and Bruch's membrane thickness may affect drug transport from sclera into inner ocular tissues. Moreover, highly lipophilic drugs may be drained into choroidal systemic circulation restricting drug molecules from reaching inner ocular tissues (retina).

Blood retinal barrier (BRB) is composed of inner and outer BRB. Outer BRB is sandwiched between choroid and retina and constitutes tight junctions of retinal pigment epithelial cells whereas inner BRB is composed of retinal capillary endothelial cells. Functions of these tight junctions are supported by astrocytes and Muller cells. Tight junctions regulate the exchange of substances between choroid and retina. Astrocytes are involved in maintaining the integrity and enhancing the barrier properties of retinal endothelial capillaries.[19,20] BRB provides protection to retina from molecules circulating in retinal circulation. Retinal endothelial cells lack fenestrations and thus transport may be mediated by receptor, energy/adenosine triphosphate dependent fluid phase pinocytosis. Therefore, drug entry is highly restricted due to the presence of tight junctions. Also, expression and activity of P-gp, MRP efflux pumps on apical and basal sides of human retinal pigment epithelium have been reported.[21-23]

Retina is the light sensitive part of the eye that lies just above the thick viscous fluid called vitreous humor. It is composed of neural and glial cells[24] and this covers the entire inner wall of the globe. It is separated from vitreous humor by presence of a thick cell layer

composed of 10 distinct extracellular matrix proteins[25] called inner limiting membrane. Drugs injected into the vitreous humor are restricted from reaching retinal cells by this limiting membrane. Intravitreally administered drugs are eliminated due to aqueous humor turnover and uveal blood flow in the anterior chamber. On the other hand, in the posterior chamber, elimination takes place by drug transport across retina. Transcellular and paracellular routes are ways to transport drugs across RPE. Hydrostatic and osmotic forces are involved in transporting molecules from subretinal spaces to RPE from where elimination occurs.[26]

Vitreous body is a clear, vascular, thick gelly like fluid that covers the space between the lens and the retina and aids in maintaining the structure of the globe. It is composed of 99.9% water, 0.01% hyaluronic acid, collagen and ions.[27,28] Diffusion in vitreous regulates the drug movement, convective flow of vitreous fails to alter drug diffusion at any significant rate.[29] Currently, the major route of drug administration to the back of the eye is by intravitreal administration. Pathophysiological state of vitreous and molecular weight of active agents determine the diffusion kinetics.

Previously described ocular static and dynamic barriers prevent administered drug from reaching the targeted tissue. In order to reach the targeted ocular tissues, molecules need to possess sufficient hydrophilic and lipophilic balance (HLB) and also evade efflux pumps expressed on the cell membrane. Drug delivery systems such as microparticles, nanoparticles, oil in water emulsions, liposomes, suspensions and nanomicelles are constantly being developed to address the above issues.

Drug Delivery in Posterior Segment of Eye

Topical drug administration

Topically administration of drug to the anterior eye has been proven successfully in the treatment of eye diseases, it can easily access to the target site. However, the adoption of similar mechanisms in topical drug penetration to the posterior segment of eye presents numerous challenges. While this is being the least invasive method of drug application, topically applied drugs permiations are prevented by many components of the anterior eye, including the corneal epithelium, corneal endothelium, conjunctiva and sclera.[30] In addition, the longer diffusion distance to the posterior eye and the acellular nature of the vitreous negatively impact the pharmacokinetics and distribution of the topical drugs.[30] Due to some common physiologic processes such as tear production, blinking, drug metabolism and drug binding also impact topical applications, hindering the access of topical drugs to the target locations. All of these factors and limitations lead to increased dosing and a higher frequency of drug application in order to attain therapeutic concentrations, making the use of topical drugs relatively inefficient for patients and leading to decreased patient compliance.

Recent research has focused on small-molecule penetration into the vitreous, with evidence that molecules with lower molecular weight have high permeability into the posterior chamber. Molecules with higher molecular weights and superior water solubility (highly charged) may have longer half-lives than those with lower molecular weights.[31] Thus, lower molecular-weight compounds have increased access to the posterior eye and may minimize the risk of toxicity compared with higher molecular-weight compounds, which degrade at slower rates. These characteristics are generalizations. Therefore, each drug must be individually assessed and its uptake, efficiency and safety must be determined.

Systemic drug delivery

The systemically application of drugs is another method of access to the posterior segment. The drugs are administered orally or intravenously, enabling distribution throughout the body via the blood-stream. From the blood, the drugs can easily enter the choroidal extravascular space as the choroid has an extensive vascular network and leaky walls. However, the entry of the drug into the posterior segment is often limited by the outer and inner blood–retinal barriers that are made up of retinal pigment epithelium (RPE) and endothelial cells of the retinal blood vessels, respectively. The RPE contains several efflux pumps including P-glycoprotein and multidrug resistance-associated protein, which reduce the permeability of various endogenous compounds into the vitreous.[32] The systemic application of drugs not only increases the quantity of a drug necessary to achieve therapeutic concentrations, but it also increases the risk of adverse effects due to the accumulation of a drug in other tissues throughout the body. Another limitation of systemic application includes potential reduced time of therapeutic effects and potency due to the dilution and degradation of the drug before reaching the target site.[33] Moreover, drug–drug interactions in patients being treated for coexisting medical conditions also influence the administration of systemic drugs for the treatment of retinal disease. A summary of the major limiting factors with topical and systemic drug administration is shown in table 1.[30]

Table 1: Limitations of topical and systemic drug administration.

Topical	Systemic
Lacrimation	Blood–retinal barrier
Aqueous production	Higher therapeutic index
Impermeability of corneal epithelium and endothelium	RPE efflux pumps: P-glycoprotein and multidrug resistance-associated protein
Blood flow	Increased drug accumulation throughout other body tissues

Other than these limitations, there have been advances in the use of systemic medications for the treatment of ophthalmic diseases. Generally, there is increasing focus on creating drug delivery methods that control the rate

and delivery time to the posterior eye, thus increasing both the belonging to both space and time efficacy and reducing drug accumulation. One major advance has been the efficacious use of the prodrug of ganciclovir, valganciclovir, for the treatment of cytomegalovirus (CMV) retinitis. Valganciclovir, which metabolizes to ganciclovir, provides an oral route of treatment for CMV retinitis as an alternative to the previously used intravenous (iv.) ganciclovir treatment.[34]

The use of newer, more potent and more soluble antibiotics might result in an increased efficacy in treating endophthalmitis. Increased penetration of some fluoroquinolones yields better treatment outcomes when compared with the aminoglycoside amikacin and cephalosporin ceftazidime.[35] Endophthalmitis treatment with fluoroquinolones is superior at targeting several strains of bacteria including *Klebsiella pneumoniae* and *Pseudomonas* spp., which are showing increasing resistance to other antibiotics, including amikacin and β-lactams.[35–37] The primary pathway for the delivery of drugs to the posterior segment, followed by different routes shown in Fig.1.

Intravitreal injection

Intravitreal injection a new means of drug delivery that is becoming more popular now a days. These involves the direct administration of drug solution/suspension into vitreous humor via pars plana using a 30-G needle in the form of solution, particles, suspension, depot or implants, into the posterior segment.[38] Many pharmaceuticals aimed for treating posterior segment of eye diseases using drug delivery via this route. Intravitreal injection provides increased drug concentrations at the neural retina and minimizes systemic side effects. Nonetheless, frequent administration of drugs via this route can lead to retinal detachment, retinal haemorrhage, endophthalmitis and increased intraocular pressure.[39,40]

In contrast to the topical and systemic routes, intravitreal injection makes high concentrations of drug locally available to the internal eye tissue, including the choroid and the retina. Anti-Vascular Endothelial Growth Factor drugs, such as pegaptanib, ranibizumab and bevacizumab are new intravitreal treatments for AMD and macular edema; intravitreal injection is currently the most acceptable and effective method to treat vitreoretinal disease. This method allows a direct application of the drug into the posterior segment of eye, thus eliminating the barriers common with topical and systemic administration. As a result, a much higher dose of drug can reach the target site and yield a more efficacious treatment of posterior eye diseases. Agents with molecular weight less than 500 Da when applied intravitreally, however, tend to be drained off from the site of application with a half-life of less than 3 days, indicating a need for repetitive injections. However, the period requiring a repeat dose may extend from a few days to several months for macromolecular antibodies Intravitreal triamcinolone acetonide is being used to treat AMD and macular edema. However, multiple injections may be necessary as a result of the limited half-life of many compounds in the vitreous, potentially causing trauma and increasing the risk of cataract, retinal detachment, hemorrhage and endophthalmitis.[33,41,42]

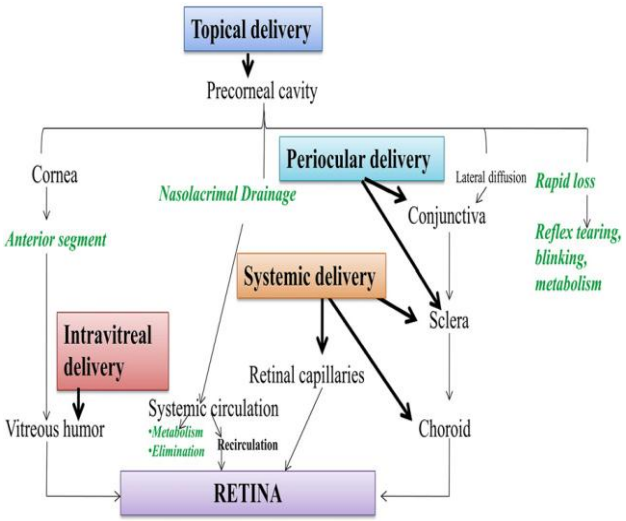

Fig 1: Pathways for distribution of drug to the retinal tissue of the eye by different delivery routes.

Ocular implants

Ocular implants provide a platform for sustained release of drugs from either biodegradable or non-biodegradable polymeric systems over several months to years.[43] Currently, there are three ocular implants,Vitrasert, Retisert and Ozurdex, approved by the FDA, with the first two being non-biodegradable systems anchored to the sclera while the latter is a biodegradable rod injected into the vitreous. Another non-biodegradable implant, Iluvien, recently got approval.

Nonbiodegradable implants

Intravitreal, transscleral and iontophoretic routes of drug administration tend to achieve high drug levels in the posterior eye and are typically more efficacious than systemic and topical methods. However, these drugs are liable to rapid clearance and require frequent administration. The half-life of most drugs in the vitreous is limited to a few hours.[44] This led to the development of sustained-release drug delivery systems that minimize the frequency of drug application and decrease the importance of patient compliance. In addition, these controlled systems deliver drug without an initial burst. Many types of controlled-release drug delivery systems have been developed, including nanoparticles, microcapsules, liposomes and implants.[45]

Many research is being working on implantable sustained-release vehicles of drug delivery. The main advantage of these implants include,to provide the opportunity for removal of the drug in case of toxicity, Specifically, when implantable device can be transfer as required; however, injectable liposomes, microparticles and nanoparticles would be difficult to be drawn back

once toxicity is marked. There are three approved implantable devices available; one is biodegradable and other two are non biodegradable polymer implants, which may achieve diffusive zero-order kinetics over a period of time. These implants are not metabolized *in vivo*, and may require replacement or removal once the drug is depleted. As a result, there has been increasing research into biodegradable vehicles that would allow the implants to be slowly converted to soluble forms via enzymatic and non enzymatic reactions in the eye.[45] This, in turn, eliminates the need for the implants to be removed and replaced in different locations and, thus, decreases side effects from multiple invasive procedures.

Biodegradable implants

The safety and efficacy of several nonbiodegradable implants have been demonstrated, the process of surgical implantation and removal has many potential deleterious side effects, including vitreous hemorrhage, retinal detachment and endophthalmitis. Inn these metho once the drug is depleted, the device may need to be removed and a new device implanted. To eliminate this, more research is focusing on the development of biodegradable implants, which are soluble and, thus, do not need to be removed or reimplanted when the drug is depleted. These implants have been manufactured in a variety of forms including rods, discs, pellets, plugs and sheets, and allow implantation through smaller incisions than the nonbiodegradable.[46]

The drugs in the biodegradable implants are conjugated to a variety of polymers including polylactic acid (PLA), polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA), polycaprolactone and polymethylene malonate.

The efficacy and safety of a biodegradable intrascleral implant were evaluated. The implant (1 mm thick × 3 mm diameter) was made of PLA (poly[D,L-lactide]) with Triamcinolone acetonide (TA) 6.4 mg.[47] The design was unique in that it utilized the high molecular weight of PLA as a one-side coating, permitting a unidirectional drug absorption in the sclera. A 12-week *in vivo* study in 20 rabbit eyes was performed to measure the efficacy of the drug reaching the vitreous. The preliminary study demonstrated statistically significant levels of TA in the aqueous humor until 4 weeks postimplantation and in the retina–choroid until 8 weeks. TA was detected constantly over the full 12-week period in the vitreous. The preliminary study shows promise for a biodegradable TA implant, and further studies are underway to determine the efficacy of such an implant in humans.[47]

Along with these benefits, there were minimal side effects of the implantation. No cases of endophthalmitis were reported, and there was no significant difference in the number of reports of cataract among the different study groups. Most cases of vitreous hemorrhage were seen within the first week after surgery and were mild in severity.

Most of these only had one occurrence of elevated intraocular pressure, and all patients were successfully managed with observation or a topical medication. The only other adverse effect to occur significantly more frequently in the treatment group was anterior chamber flare. A total of 5% of patients in the 700-µg group were observed to have anterior chamber flare, while 0% was seen in the control group. These adverse effects seem minimal compared with trials of flucinolone acetonide (FA) implants; however, it must be noted that the follow-up periods in this study were also shorter.

Transscleral diffusion

This is relatively a newer method of drug delivery, a less invasive method in which the drug permeates through ocular tissues to reach the neuroretina. Transscleral delivery includes such avenues as subconjunctival, retrobulbar, peribulbar, sub-Tenon's and intrascleral delivery.[33] An overview of these avenues of application is presented in table 2.[48]

Table 2: Overview of transscleral drug delivery techniques.

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, ptosis 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.
Sub-Tenon'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.

Although transscleral methods eliminate some of the side effects of intravitreal delivery, but they 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, require very high doses to be effective. These barriers are categorized into three major groups: static, dynamic and metabolic as shown in table.3.[48]

Table 3: Barriers to transscleral drug delivey.

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	Transport proteins, drug efflux pumps and ion transporters	

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.[49] The radius of the molecule plays a major role in predictor of permeability than the weight and charge.[50] Finally, the solubility of the drug compounds is impacted by the water and lipid interactions.The 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.[50] However, a balance may be critical since many lipophilic compounds can easily penetrate the RPE; a problem can arise owing to toxicity caused by a 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; however, this method provides barrier and permeability limitations.

Transscleral iontophoresis

This is another transscleral method which involves an electrodynamic process of drug delivery termed iontophoresis. In this technique, charged molecules are delivered across the sclera and into the posterior chamber of the eye via a direct electric current. In most cases, an iontophoretic probe is placed over the pars plana, enabling a bypass of the lens–iris barrier. This arrangement permits the precise delivery of high quantities of drugs through changes in the intensity of the applied current, yielding improved control of constant, uniform drug delivery. Animal and human studies have shows that iontophoresis have less side effects in compare to intravitreal injections and may improve the efficacy of periocular injections by decreasing the risk of retinal detachment, endophthalmitis, globe perforation and ptosis.[51] In effect, iontophoresis reduces the risk of injections and surgical procedures. Iontophoresis is beign to be successful in delivering biologically relevant concentrations of numerous ophthalmic drugs including corticosteroids, antibiotics, anti-inflammatory agents and immunosuppressants.[51]

In iontophoretic device, the main elements impacting the amount of drug delivery is the amount of current, concentration of drug, the duration of treatment, pH of the drug and the permeability of the tissue.[33] Another major concern is that the resistance in the tissue may change over time after repetitive applications of current and heat, altering the electrical field and leading to changes in drug permeation, thus altering drug peaks and troughs.

Several types of iontophoretic devices are available and each provides its own set of benefits,For example, the coulomb-controlled iontophoresis unit allows an automatic adjustment in electrical current based on the changes in resistance across the conjunctival epithelium.[51,53] This unit also provides self-calibration and acts as an indicator for proper electrical probe contact.[51,53] Other iontophoretic units include the mini-

ion unit and the EyeGate® II iontophoresis device.[51] The portable mini-ion unit provides a variable electrical current for a preset amount of time. It uses a hydrogel probe to deliver charged drugs to the posterior eye.[54,55] The EyeGate II device is a new, updated version of the original EyeGate iontophoresis device. The EyeGate II uses an electrical current to hydrolyze water and, thus, increase ion mobility, allowing greater concentrations of drug to reach the posterior eye. As the current induces like-charged ions to repel each other, more drugs are delivered through tissues.

Research and development of new intravitreal, transscleral and iontophoretic drug delivery methods continue with the goal of optimizing therapeutic drug concentrations while minimizing risks and side effects.

Thermoresponsive gels

Hydrogels have been proposed as an alternative method of delivering anti-Vascular endothelial growth factor (VEGF) drugs to the posterior eye. Anti-VEGF therapies may not be effective in eyes after vitrectomy owing to a shortened half-life time in the vitreous cavity. A recent study examined the use of thermoresponsive gels for the delivery of anti-VEGF for the regulation of angiogenesis. VEGF acts as an endothelial cell mitogen and increases vascular permeability. VEGF is known to be increased in diabetic retinopathy and AMD.

They are used as it can prolong the drug residence in the vitreous even after vitrectomy; this could provide potential treatment benefits. Hydrogels are polymeric networks and absorb large amounts of water while remaining insoluble in aqueous solutions. Hydrogels permit the manipulation of permeation and diffusion characteristics, allowing the optimization of drug delivery. As these hydrogels do not have hydrophobic interactions that normally denature biomolecules which is excellent for encapsulating biomacromolecules including proteins and DNA. In addition when compared with hydrophobic polymers such as PLA or PLGA, the formation of hydrogels usually occurs at ambient temperatures and organic solvents are rarely needed. Hydrogels can be made from natural or synthetic polymers, each with its own benefits and drawbacks. Natural polymers provide increased biocompatibility, biodegradability and biologically recognizable moieties that support cellular activities; however, at the same time they do not provide the mechanical properties that synthetic polymers possess and they may evoke inflammatory responses within the body.[56]

The main factor that determines the degree of hydrophilicity of hydrogels is the nanostructure of cross-linked hydrogel networks. This nanostructure consists of three major factors: polymer volume fraction in the swollen state, number of average molecular weight between cross-links and network mesh size. The manipulation of these factors allows scientists to develop hydrogels for various drug delivery targets. The hydrophilicity of hydrogels provides an increased *in vivo* circulation time as a result of evading host immune responses and decreasing phagocytic activities.[56,57] In addition, hydrogels can be made to be bioadhesive, thus facilitating drug targeting through mucus membranes for noninvasive drug administration. Finally, hydrogels permit various mechanisms of drug release, including diffusion-controlled, swelling-controlled and chemically controlled drug release.

Accordint to recent scientific evidence the potential of hydrogels as a drug delivery vehicle for molecules to reach a target site through an external stimulus such as temperature, pH, glucose or light. These hydrogels are biocompatible and biodegradable in nature and are considered a useful tool in nano-drug delivery, and have applications in the field of sustained-release drug delivery.

Nanotechnology

This section provides an introduction into the types of nanoparticlesor technologies that have been investigated for posterior segment diseases.

Polymeric nanoparticles

Polymeric nanoparticles can be studied extensively as targeted and sustained drug delivery systems for effective drug delivery to the target with minimum side effects Polymeric nanoparticles (PNPs) are polymeric colloidal particles which can adsorb, absorb, attach, or encapsulate (dissolve or disperse) drug molecule.[58] PNPs have been engineered from various synthetic and natural biocompatible polymers. PNPs derived from natural materials like albumin can serve as an efficient drug delivery system as they are biodegradable, nontoxic, and nonimmunogenic. Albumin also has a high content of charged amino acids, which permits attachment of positively or negatively charged drugs and oligonucleotides[59] on it. The most commonly used synthetic polymers are polylactide (PLA) and poly(lactide-co-glycolide) (PLGA), which degrade in vivo to form natural metabolites (lactic and glycolic acids) that are eliminated from the body through the Kreb's cycle. Their degradation rate can be tailored via changes in co-polymer composition, a molecular weight and a conformation that can provide controlled drug release ranging from months to years.[60–62] Being biocompatible, biodegradable, nontoxic, and nonantigenic, numerous PLGA containing therapeutics are approved by FDA.

PNPs offer numerous advantages of controlled ocular drug release as demonstrated below in Table 3 and also in the following illustration. Fluorescent-labeled PNPs were found to be internalized into the retina and remained in the RPE cells for 4 months with no toxic effect following a single intravitreal injection.[63] Thus, PNPs can provide a steady and continuous delivery of drugs simultaneously avoiding the requirement for

repetitive administration and hence intraocular surgical procedures.

Zhang et al.[64] showed that the dexamethasone-PLGA nanoparticles sustained the drug release for at least 50 days in the rabbit eyes, during which relatively constant drug levels were obtained for about 30 days, in the vitreous, with the mean concentration of 3.85 mg/L.

Concentration in vitreous was significantly higher than in the plasma, indicating minimum systemic side effects. PNPs improve residence time and their ability to target drugs to the sight of action leads to a decrease in the required dose[65] and dosing frequency.

Liposomes

Liposomes are biocompatible and biodegradable lipid network comprising of an aqueous volume surrounded by a phospholipid bilayer, with drugs entrapped in the core or bilayer.Liposomes can vary in size from micrometers to nanometers. They can be uni-or multilamellar, and can vary considerably in their size, surface charge, lipid composition, fluidity of the bilayers, and method of preparation. Liposomes are versatile in drug loading properties. For instance, they can encapsulate hydrophilic drugs in the core and lipophilic drugs in the bilayer. Ionic drug loading can be further facilitated by using cationic or anionic lipids. The encapsulated drug is usually released by passive diffusion, vesicle fusion, or vesicle disruption. Further, intravitreally delivered liposomal formulations have also been found to have minimal tissue toxicity and enhanced drug vitreal half-life by reducing drug elimination from the vitreous cavity.

Intravitreally administered liposomal systems not only increase drug t1/2[66] but also minimize any intraocular side effects associated with the use of entrapped agents.[67] Radiolabeled oligonucleotide ([33P]pdT16) liposomes showed a significantly longer retention than the free oligonucleotide solution in the vitreous chamber. This was attributed to the decrease in the degradation[68] of oligonucleotide entrappedwithin the liposomes. After 24 h of administration, the residual concentration of pdT16 within the vitreous was 9.3-fold higher when administered as a liposomal suspension in comparison to the free pdT16 solution.

A single intravitreal injection of liposome-encapsulated cidofovir prevented Herpes simplex virus retinitis for 4 months[69] in experimental model of HSV-1 retinitis. This demonstrates that a sustained release of the drug in the posterior segment is possible froma liposomal carrier and it could be a viable option for treatment of retinal diseases. The presence of intact liposomes in retina after topical delivery, on the other hand, was indicated by Hironaka et al.[70,71] They proposed that the liposomes travelled majorly through the corneal and conjunctival route involving the iris and ciliary body. Such a transport mechanism was attributed to the rigidity and nano size of the liposomes. It was found that fluorescent liposomes prepared using L-α-distearoylphosphatidylcholine showed higher fluorescence emission in the retina than those prepared using egg phosphatidylcholine, and that the former were more rigid than the latter. Rigidity maintains the stability of the carrier system in the biological environments such as tear film and ocular mucosa.

Tremblay et al.[66] found that the ocular toxicity was significantly reduced when liposome-intercalated amphotericin B was intravitreally injected as compared to commercial amphotericin B (for intravenous use which contains sodium desoxycholate as a solubilizing agent).

Nanomicelles

The molecules belonging both hydrophilic and hydrophobic groups is called as an amphiphilic molecule. These molecules when allowed to react with a suitable solvent orient to form normal or reverse nanomicelles, depending on the type and degree of orientation. The hydrophilic portion orients towards the polar solvent whereas the hydrophobic section of the molecule orients away from the solvent. This orientation results , the hydrophobic parts are gathered in the core while the hydrophilic portions are allied towards the outer surface to maximize contact with water.[72,73] Such aggregates are termed as normal nanomicelles. On the other hand, amphiphilic molecules undergo an opposite orientation mechanism to form reverse micelles. When the amphiphilic molecule exposed to a hydrophobic solvent system, the amphiphiles tend to form nanomicelles with hydrophobic region towards outside and the hydrophilic portion towards inside. Normal nanomicelles can be used to encapsulate, solubilize and deliver hydrophobic drugs. While reverse nanomicelles can be applied to encapsulate and act as better candidates for delivery of hydrophilic drugs.[74] Nanomicelles serve as excellent drug delivery systems owing advantage to minimize drug degradation, reduce adverse side effects and improve drug bioavailability.[75–77] In ocular drug delivery, nanomicelles offer unique advantages due to their nanoscale size, aqueous clear/transparent drug formulation, encapsulate and solubilize hydrophobic drugs and enable high permeation through ocular epithelia with minimal or no irritation. Nanomicelles can be formed with either surfactants or polymeric systems.

Nanoemulsions

Nanoemulsions consist of two immiscible liquids in which one liquid is dispersed as droplets in another liquid[78] stabilized by the use of surfactants. These homogeneous systems, which can be prepared over a wide range of surfactant concentrations and oil to water ratios, are all fluids of low viscosity, thus applicable for topical administration to the eye. The surfactant in combination with co-surfactant lowers the interfacial tension which ultimately facilitates dispersion process during the preparation of nanoemulsion and provides a

flexible film that can readily deform around the droplets.[79] In the presence of a surfactant and cosurfactant increases membrane permeability, thereby increasing drug uptake. Hence, these systems act as penetration enhancers facilitating their own corneal uptake.[80] The choice of surfactant, oil, co-surfactant is important since these ingredients need to be nonirritating and nontoxic to the corneal surface and other ocular tissues.

In addition to this, nanoemulsions provide sustained release of the drug, high penetration in the deeper layers of the ocular structure, ease of sterilization,[81] low viscosity, and their capacity to accommodate both hydrophilic and lipophilic drugs. Thus, these systems can achieve a faster therapeutic action with a smaller dose resulting in fewer systemic and ocular side effects. The latter may also result from a decreased need to repeat the applications per day. This factor also tends to enhance better patient compliance.[82] However, only a single study report by Hagigit et al.[83] proclaimed the protection of oligonucleotide (ODN 17) by its entrapment in nanoemulsion fromvitreous degradation and presence in retina even 3 days after its intravitreal injection.

Nanosuspension

A pharmaceutical nanosuspension is defined as very finely dispersed solid drug particles in an aqueous vehicle for either oral and topical use or parenteral and pulmonary administration. The particle size distribution of the solid particles in nanosuspension is between 200 and 600 nm. Nanosuspension are different from nanoparticles. Nanoparticles are commonly polymeric colloidal carriers of drugs whereas solid lipid nanoparticles are lipid carriers of drugs. In nanosuspension technology, the drug is maintained in the required crystalline state with reduced particle size, leading to an increased dissolution rate and improved bioavailability. An increase in the dissolution rate of micronized particles (particle size < 10 μm) is related to an increase in the surface area and consequently the dissolution velocity. Nanosized particles can increase solution velocity and saturation solubility because of the vapor pressure effect. In addition, the diffusional distance on the surface of drug nanoparticles is decreased, thus leading to an increased concentration gradient.

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants. They can also be defined as a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the suspended particle is less than 1 μm in size. Nanosuspensions can be used to enhance the solubility of drugs that are poorly soluble in aqueous as well as lipid media. As a result, the rate of flooding of the active compound increases and the maximum plasma level is reached faster (e.g., oral or intravenous [IV] administration of the nanosuspension). This is one of the unique advantages that it has over other approaches for enhancing solubility. It is useful for molecules with poor solubility, poor permeability or both, which poses a significant challenge for the formulators. The reduced particle size renders the possibility of intravenous administration of poorly soluble drugs without blockade of the blood capillaries. The nanosuspensions can also be lyophilized or spray dried and the nanoparticles of a nanosuspension can also be incorporated in a solid matrix. Apart from this, it has all other advantages of a liquid dosage form over the solid dosage forms. The present review is focused on various methods of preparing nanosuspensions, critical parameters to be characterized and the application of nanosuspension formulations.

Maheswari *et.al*, studied the nanosuspensions were prepared by the solvent displacement method using acetone and 1% (w/v) Pluronic® F108 solution. Physicochemical characterization of the nano suspension was performed by measuring particle size, zeta potential, drug entrapment efficiency and in vitro drug release. The delivery system was intended to enhance ocular availability without blurring vision and reducing the frequency of dosing in conjunctivitis leading to patience compliance. Positive surface charge of nanoparticles can allow longer residence time for the drug on the eye surface by increasing the interaction of nanoparticles with the glycoprotein of the cornea and conjunctiva.[84]

Nanospheres

Nanospheres have also been used to target the RPE for sustained drug delivery. Sakurai *et.al.* studied about the intraocular kinetics of nanospheres and found that polystyrene nanospheres containing fluorescein (2 μm in diameter) were detectable in the retina, vitreous and trabecular meshwork more than 1 month following an intravitreal injection *in vivo* in rabbits.[85] Bourges *et al.* showed that the feasibility of targeting the retina and the RPE using a single intravitreal injection of polylactide nanoparticles loaded with the dye, rhodamine 6G and Nile Red, which quickly accessed the retina and were observed for 4 months post injection[86] Anionic nanoparticles traversed the collagen fibrils of the vitreous more readily than the cationic nanoparticles, showing potential as drug delivery vehicles for the subretinal space and the RPE. Müller cells take up the nanoparticles, possibly playing a key role in retinal penetration. Gaudana *et al.* reported that ligands, such as folate and biotin, attached to the surface of steroidal nanoparticles, can increase uptake by the RPE.[87]

CONCLUSION

Ocular drug delivery has become an increasingly important field of research. Advances in the ocular drug delivery systems research are expected to provide new tools for the treatment of the eye diseases with the new therapeutic modalities. These delivery methods should provide prolonged action, less invasive administration, higher efficacy, and improved safety.

In this article we describe just a few promising studies about drug routes or delivery to posterior segment of eye from vast source conducted within the area of intersts. Although it may be some time before many or any of these technologies are available, this review may provide a sense of hope, to know that so much change is taking place in the field of ocular drug delivery.

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