2. Transscleral drug delivery to the posterior segment of the eye: Particulate and colloidal formulations and biopharmaceutical considerations

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Abstract. Diseases or disorders affecting the posterior segment of the eye, such as diabetic retinopathy, age related macular degeneration and retinitis pigmentosa, are the leading causes of decreased visual acuity and blindness. Successful treatment modalities require generation and maintenance of therapeutically effective drug concentrations at the target sites: vitreous, retina and/or choroid. Drug delivery to the posterior ocular segment is, however, limited by several physiological processes. Topical instillation, the most favored local mode of application, is challenged by tear flow, structural complexity of the cornea, diffusion distance, counter-directional intraocular convection and conjunctival, scleral and choroidal vasculature and lymphatics. Although systemic administration offers an alternative route, the blood-ocular barriers restrict the diffusion of a wide variety of...
therapeutic agents from the systemic circulation into the ocular chambers. In recent years, transscleral delivery approach has gained in prominence rapidly. A relatively large scleral surface area with favorable permeability characteristics presents opportunities for efficient and effective delivery to the retina and vitreous. This chapter will explore the recent literature on transscleral drug delivery and disposition, with a particular emphasis on novel drug delivery systems like particulate and colloidal formulations.

1. Introduction

Diseases affecting the posterior segment ocular tissues are the major causes of impaired vision and/or blindness around the world. In the United States (US) itself, approximately 0.78% (937,000) of those over the age of 40 years are blind and this number is projected to increase by 70%, to 1.6 million, by the year 2020 [1]. The leading causes of blindness are age-related macular degeneration (AMD), cataract and glaucoma, in addition to other diseases like diabetic retinopathy and retinal degeneration [1]. It is estimated that about 1.47% (1.75 million) of the population in the age group of 40 years and older in the US is diagnosed with AMD and this number may reach 3 million by 2020 [2]. Further, approximately 4.1 million US adults aged above 40 are suffering from diabetic retinopathy and one out of every 12 persons with diabetes mellitus, in this age group, faces vision threatening retinopathy [3]. Although significant progress has been made in the identification of molecular mechanisms involved and in the development of therapeutic agents, drug delivery to the posterior segment of the eye, or back-of-the-eye, remains a formidable challenge for the pharmaceutical scientists.

Topical instillation, the most favored route of delivery for ocular diseases, is rather ineffective in generating appreciable drug concentrations in the posterior segment. This approach faces several mechanisms that lead to drug loss. Precorneal drainage reduces the effective contact time between the drug and the corneal epithelium and, thus, decreases the amount absorbed. Moreover, the structural characteristics of the corneal epithelium limit transcorneal solute flux. The low fluid holding capacity of the cul-de-sac, about 30 µL, is another limiting factor. A major fraction of the drug is also lost into the systemic circulation through the conjunctival vasculature or nasolacrimal duct. It has been estimated that only 5% of the topically applied drug essentially reaches the cornea and eventually the intraocular tissues [4, 5].

Intravitreal injections and intrascleral and intravitreal implants can effectively deliver therapeutic agents to the back-of-the-eye. However, these methods are invasive and lack of patient compliance, in addition to associated risk factors such as retinal detachment, endophthalmitis and cataract, make them less attractive choices. An alternate route by which therapeutic agents
can reach the posterior segment of the eye is by diffusion across the endothelial lining of the retinal and choroidal blood vessels following systemic administration. However, in this case, the molecules encounter the blood-retinal-barrier (BRB) comprised of the endothelial cells of retinal capillaries and the epithelial cells of retinal pigmented epithelium [6]. The BRB acts as a significant diffusional barrier, a characteristic dependent on the physiochemical properties of the compound and its interaction with BRB efflux proteins. Moreover, compared to topical instillation, significantly greater doses have to be administered systemically in order to generate the targeted therapeutic concentrations in the eye, if at all possible. This can lead to nonspecific systemic exposure and consequential side-effects.

In recent years, drug delivery across the sclera for various retinal and uveal disorders has attracted a lot of attention and interest among pharmaceutical scientists and a large number of reports investigating the feasibility of these approaches have appeared in the literature [7-14]. From a drug delivery standpoint, the transscleral route offers quite a few advantages: i) high scleral surface area, which can increase the rate and extent of absorption; ii) high degree of hydration, which is conducive to the diffusion of hydrophilic molecules; iii) metabolic inactivity, which can facilitate delivery of agents sensitive to metabolic enzymes [15]; iv) relatively high permeability to macromolecules [7, 13] and v) feasibility of administering controlled and sustained release dosage forms [16]. Additionally, Olsen et al. observed that scleral permeability did not change with the age of the patient. This is very significant as age is a major factor in the pathogenesis and progression of AMD and diabetic retinopathy [13].

Advances in colloidal drug delivery systems demonstrated significant promise with respect to enhancing the oral and systemic bioavailability of numerous drug molecules. In the recent past, the feasibility and superiority of these delivery systems for topical delivery targeting the anterior ocular segment has been demonstrated [17, 18]. However, very few reports investigate the utility of transscleral application of colloidal drug delivery systems for posterior segment diseases. This chapter discusses the diverse aspects of transscleral drug delivery including physiological barriers encountered, sites of application, pharmacokinetic models and application of colloidal drug delivery systems for posterior segment ocular diseases.

2. Anatomy of the human sclera

Sclera is the opaque outer tunic of the eye. It extends posteriorly from the outer ring of the cornea to the optic foramen, and is perforated by the optic nerve. The mean human scleral surface area is 16.3 cm² [15]. The thickness
of the adult human sclera is not uniform, increasing gradually as one approaches the optic nerve. It is thickest at the posterior pole (1-1.35 mm), thinner at the equator (0.4-0.6 mm) and thinnest under the recti muscle (0.3 mm), but again increases to 0.6 mm at the region where the shiny tendon fibers merge with scleral collagen. In the region where it blends with the cornea it measures up to 0.8 mm in thickness. Human scleral thickness shows gender variation with the female sclera being thinner than that of the male. Scleral thickness and opacity increases with age [19, 5].

The scleral tissue possesses considerable visco-elastic properties and consists of the tenon’s capsule, the episclera, the stroma, the spur and the lamina fusca [19]. The tenon’s capsule and the episclera are the two outermost vascularized layers of the sclera. The stroma is composed of collagen and elastic fibers. The lamina fusca forms the outer portion of the choroid and is a component of both the uveal tract and the sclera [5, 19]. The spur is a rigid ring like structure formed by the abridgment of the deep scleral fibers with the fibers of the limbus. The sclera is mainly made up of collagen fibrils, predominantly Type I collagen, embedded in a glycosaminoglycan (GAG) matrix. In addition, collagen Types III, V, VI, VIII and XII are also found in the human sclera. Based on the structure and composition of the sclera it is believed that hydrophilic drugs are better suited for transscleral diffusion [5].

3. Transscleral drug delivery

Transscleral drug delivery approaches include subconjunctival, subtenon, retrobulbar, peribulbar, and juxtascleral administration (Fig. 1). The following sections briefly discuss the various transscleral modes of application and the few literature reports exploring these approaches for drug delivery to the posterior segment.

3.1. Subconjunctival route

Subconjunctival injection involves administration below the conjunctiva. Through this route, volumes up to 500 μL can be administered. Following subconjunctival placement, there are three possible pathways through which the administered drug can gain access into the vitreous humor [20]. The first constitutes direct diffusion wherein the compound traverses across the underlying tissues into the vitreous humor. An alternative pathway could be absorption into the aqueous humor followed by diffusion into the vitreous humor. Thirdly, the drug moiety could be absorbed into the general systemic circulation, through the scleral, conjunctival and soft tissue vasculature
vasculature and lymphatics, and then diffuse across the BRB into the vitreous humor. Lee and Robinson evaluated the contribution of each of these three pathways and found that only the first contributes significantly to the overall vitreal bioavailability of the administered drug. Although the subconjunctival route does deliver the compound into the aqueous humor and the systemic circulation, the contribution of these routes to drug penetration into the vitreous humor is minimal [21].

Several studies have demonstrated the utility of the subconjunctival route for delivering therapeutic agents to the back-of-the-eye [22-25]. Weijtens et al. determined the pharmacokinetics of dexamethasone sodium phosphate following subconjunctival, peribulbar and oral administration in patients suffering from rhegmatogenous retinal detachment [26]. The subconjunctival route was observed to be the most effective as it yielded a significantly higher $C_{\text{max}}$ value in the vitreous humor, compared to the peribulbar and oral routes. Chervu et al. [27] evaluated vitreal bioavailability, following subconjunctival application, of three molecules of different lipophilicities: sodium fluorescein, budenoside, and celecoxib (logP values -0.67, 3.2 and 4.0, respectively) in rats. However, a correlation between the logP values and the retinal concentrations generated (budenoside > sodium fluorescein> celecoxib) for the three molecules was not apparent. In another study, Ayalasomayajula et al. [9] demonstrated the efficiency of the subconjunctival
route over the intraperitonial route for vitreal delivery of celecoxib. Subconjunctival administration produced about a 54-fold higher drug concentration in the ipsilateral eye, compared to the intraperitonial route. Moreover, the ocular tissues from the contralateral eye of the rats administered a subconjunctival dose (3 mg/rat) exhibited celecoxib concentrations equivalent to those observed following an intraperitonial administration (3 mg/rat).

Diabetes, a predisposing condition for certain eye diseases such as diabetic retinopathy and age-related macular degeneration, can potentially compromise the barrier properties of the BRB. Cheruvu et al. [28] determined the effect of diabetes on the transscleral delivery of celecoxib to the retina, following subconjunctival injection. The results indicate an increase in the AUC of celecoxib in the retina and vitreous humor. A more pronounced effect was observed in the Brown Norway (BN) strain than in the Sprague-Dawley (SD) strain. Ratio (diabetic/control) of celecoxib in the ipsilateral eye was 1.6 and 2.44 in the SD and BN strains, respectively. The authors attributed the observed effects to increased permeability of the BRB. This phenomenon was further supported by 4 kD FITC-dextran leakage assay which revealed that the BRB leakage was 1.5 fold higher in the diabetic BN rats than in the diabetic SD rats. The same research group also demonstrated that the retinal and vitreal availability of celecoxib was reduced as a result of drug binding to melanin present in the choroid-RPE tissue [29]. Thus disease states may affect transscleral drug delivery and this needs further exploration.

3.2. Subtenon route

The tenon’s capsule, a fascial sheath of connective tissue, located between the eye globe and extra-ocular tissues, extends from the limbus of the eye anteriorly to the optic nerve posteriorly. The subtenon’s space, is located between the tenon’s capsule and the episclera [30]. Subtenon injection involves introduction of the drug solution into the tenon’s cavity around the upper segment of the eye and into the belly of the superior rectus muscle. The injection volumes range from 1-5 mL and even higher volumes can be retained in the subtenon’s space [31]. This is the most common route of administration for anesthetics. However, it is sometimes associated with subconjunctival hemorrhage.

Triamcinolone acetonide (TA) is widely used for the treatment of chronic uveitis, and cystoid macular edema (CME). Ophthalmic surgeons generally administer it either by posterior subtenon or intravitreal injection. Recently, Choudhary et al. [32] compared the efficacy of posterior subtenon injection against intravitreal injection in the management of bilateral macular edema.
secondary to idiopathic intermediate uveitis. TA was administered to the patients as an intravitreal injection (4 mg/0.1mL) in one eye and as a posterior subtenon injection in the other eye (20 mg/0.5 mL). The results revealed that both treatments were equally effective in the management of the disease. However, results from another prospective study carried out in 2005 by Bonini-Filho and coworkers [33] suggest that an intravitreal injection is more effective than the subtenon approach in the management of refractory diffuse diabetic macular edema (DME). The authors have cautioned, however, that the study was conducted in a small group of patients.

3.3. Retrobulbar route

Retrobulbar injection delivers the formulation into the conical retrobulbar cavity formed by the four rectus muscles and their intermuscular septa. Higher local drug concentrations can be achieved with retrobulbar injection for anesthesia or akinesia of the eye during surgery. With this route of delivery the effect on intra-ocular pressure (IOP) is very low or negligible [34]. Injection volumes of 2-3 mL can be administered [35]. The retrobulbar route is favored when the drug needs to be in close proximity to the macular region e.g. corticosteroids in the treatment of CME. Localization of a corticosteroid, TA, following retrobulbar injection was evaluated by Tolentino et al. and was found to be comparable to that following subtenon injection [36]. Studies with plasminogen kringle 5 (K5), a hydrophilic protein molecule and an angiogenesis inhibitor, also demonstrated that both the retrobulbar and the subconjunctival routes are effective in delivering the drug to the retinal vasculature. However, it has been suggested that the retrobulbar route will probably be more efficient than the subconjunctival route for the delivery of protein-polymer implants, taking into consideration the higher volume of this cavity [24].

3.4. Peribulbar route

Peribulbar injection was developed as an alternative to retrobulbar injection which is associated with the risk of injury to the intraorbital structures. In this case, the injection is administered at a point peripheral to the boundaries of the four rectus muscles and their intramuscular septa and can be further classified, based on the injection depth, as circum-ocular (sub-tenon’s, episcleral); peri-ocular (anterior, superficial); peri-conal (posterior, deep) and apical (ultra deep). This route can accommodate up to 8-10 mL injection volumes [37]. The peribulbar route of administration is less effective than the retrobulbar option; nevertheless, this is a safe mode of administration [34, 35].
3.5. Posterior juxtascleral

This technique was developed very recently for delivering the therapeutic agent in close contact with the sclera, especially near the macula, without puncturing the eye ball [38]. The drug loaded formulation is deposited near the sub-tenon’s space adjacent to the macula using a specialized cannula. Clinical safety and efficacy of this approach was investigated in a clinical trial involving 128 patients suffering from subfoveal exudative AMD at 18 different sites in the US and EU. An independent safety committee reviewed the safety reports and reported no clinically significant safety issues related to this mode of administration [39]. Furthermore, recently, a prospective study evaluated the efficacy of posterior juxtascleral administration of TA infusion. It was found to be effective in treating diffuse diabetic macular edema unresponsive to laser photocoagulation [40].

4. Drug delivery pathways and transport barriers in transscleral drug delivery

The above discussion serves to underline the feasibility of transscleral drug delivery approach. However, this route faces three types of physiological barriers: physical, vascular/lymphatic, and metabolic [41]. The various characteristics of these barriers and their potential influence on transscleral drug diffusion are briefly discussed below.

4.1. Physical barriers

The ocular tissues sclera, choroid, and retinal pigmented epithelium (RPE) together constitute the physical barrier to transscleral diffusion. The scleral matrix, composed of proteoglycans and collagen fibers, can hinder the permeation of solute molecules. The choroid together with the underlying Bruch’s membrane, composed of lipids and lipoproteins, can also restrict passage. The innermost physical barrier, the RPE, forms the cellular barrier, posing an obstacle to paracellular transport (with its tight junctions) and transcellular diffusion of efflux protein substrates.

4.1.1. The sclera

Several researches have investigated transscleral diffusion [10, 42, 14, 43-46], some laying special emphasis on the physicochemical characteristics of the diffusant: molecular weight (MW) [47, 7, 13], molecular size [7], hydrophilicity/lipophilicity [48] and other factors [13, 49]. Different types of
apparatus, such as modified Ussing chamber [48] and side-bi-side™ diffusion apparatus [50, 51] have been used to characterize diffusion across the sclera in vitro. Some of the important findings, with respect to drug delivery, are presented below.

An inverse relationship between transscleral permeability and solute molecular weight has been observed [13, 7, 52, 53]. However, Ambati et al. reported that the molecular radius is a better predictor of permeability across the sclera compared to the molecular weight. The authors found that the globular proteins were more permeable than the linear dextrans of the same molecular weight [7]. Furthermore, Cheruvu and Kompella [48] reported that hydrophilic molecules exhibited higher permeability than lipophilic molecules of similar molecular radii (0.53-0.57) which is consistent with reports from other researchers [43, 54]. Additionally, negatively charged molecules show higher permeability than positively charged molecules [12]. Age seems to have little effect on the permeability characteristics of the sclera. Olsen et al. found no significant correlation between age and permeability; however, very young, 9-day-old, sclera did show a higher permeability compared to the sclera from older donors [13]. Elevated intraocular pressure (15, 30 and 60 mm Hg), however, had a significant effect on the transscleral permeability of solute molecules [49]. Nevertheless, the authors concluded that this effect was minimal for the small molecules tested since the largest difference was only a two-fold increase. Boubriak et al. demonstrated the importance of hydration for transscleral permeation of hydrophilic molecules [55]. Cross linking of the sclera with glutaraldehyde resulted in decreased diffusion and partition coefficients for molecules with MW greater than 3 kD demonstrating the importance of scleral hydration in the transscleral permeation of hydrophilic molecules. Removal of glycosaminoglycan (GAG) had no significant effect on either of the parameters; probably because of lower concentrations of scleral GAG compared to cornea or other connective tissues.

4.1.2. Retinal Pigmented Epithelium (RPE) and Choroid-Bruch’s membrane

The RPE is a monolayer of highly specialized cells located between the neural retina and the choroid and forms a formidable barrier to the diffusion of hydrophilic molecules by virtue of the tight junction proteins [6]. Bruch’s membrane is the innermost layer of the choroid and also acts as a barrier to the entry of solute molecules. Cheruvu and Kompella [48] demonstrated that, compared to the sclera, the Choroid-Bruch’s layer preferentially binds lipophilic drugs, and is thus a bigger barrier to the diffusion of lipophilic
molecules than the sclera. The choroid-Bruch’s layer, however, offers little resistance to the penetration of hydrophilic and anionic molecules. The RPE and the Bruch’s membrane thus together form a major barrier to the diffusion of both hydrophilic and hydrophobic molecules. Our own studies revealed that permeability of hesperidin, a bioflavonoid, was 10-fold lower across the sclera-choroid-RPE compared to the sclera alone [50].

Changes in the morphology of Bruch’s membrane, associated with aging, can affect the diffusion of solute molecules and its effect on permeation characteristics of the membrane has been studied [56-60]. It has been observed that solute permeability decreases linearly with age. Moore et al. [57] demonstrated that age can affect the permeability of macromolecules across Bruch’s membrane. Hussain et al. [56] documented that increasing thickness of the Bruch’s membrane is capable of decreasing exponentially the diffusion of even small molecular weight compounds. Pitkanen et al. [61] observed a log linear relationship between the permeability and molecular radius of carboxyfluorescein and FITC-dexters across bovine RPE-choroid; transport decreasing with increasing molecular radius.

The RPE acts as a significant barrier to the delivery of hydrophilic agents and macromolecules, which is evident from the permeability values of a range of β-blockers having diverse lipophilicities. However, hydrophilic β-blockers exhibited shorter permeation lag times than lipophilic β-blockers; this may be because of higher affinity of lipophilic molecules to melanin present in the RPE and choroid [61].

A number of nutrient influx and efflux transporters have also been identified and functionally characterized on the blood retinal barrier (BRB) [6]. Drug moieties that are substrates of efflux pumps (P-gp, MRP, and BCRP) expressed on the RPE may exhibit compromised ocular bioavailability [62, 6]. Influx transporter targeted prodrugs may be an approach to overcome the barrier properties of these efflux transporters [63, 64]. Moreover, we recently demonstrated that topical application of inhibitors can block P-gp expressed on the RPE [65]. Thus, this strategy can also be used to modulate the efflux protein activity at the BRB.

4.2. Vascular/lymphatic barriers

These barriers mostly involve loss of the drug into the systemic circulation and lymphatics, choroidal and conjunctival/episcleral clearance, uveoscleral outflow and due to hydrostatic and osmotic pressure differentials [66, 41]. The choroidal region of the eye has the highest per unit blood volume [66]. Thus, for drugs passing across this region, the choroid is considered to act as a sink because of the huge network of blood capillaries:
the choroidal capillaries. The conjunctiva is another highly vascularized area of the eye. Conjunctival and episcleral blood capillaries together with the lymphatic network of the conjunctiva contribute to the removal of the drug and thus restrict diffusion of the therapeutic agents into the inner ocular tissues.

Effect of choroidal and conjunctival blood circulation on drug clearance was studied by Kim et al. [67]. A 30-fold higher drug concentration was observed in enucleated rabbit eyes compared to live rabbit eyes, signifying the influence of both choroidal and conjunctival blood flow on drug clearance. A recent study involving transscleral delivery of oregon-green labeled triamcinolone acetonide (OGTA) reported that both choroidal and conjunctival blood flow played a significant role in decreasing drug availability following subtenon injection [68]. Interestingly, Ghate et al. [69] observed that drug clearance in orbital and conjunctival blood vessels and lymphatics was more significant compared to clearance in choroidal vasculature. Similarly, Robinson et al. [70] studied transscleral delivery of triamcinolone acetonide and evaluated the mechanism of clearance of this compound following subtenon injection. The results suggested that the conjunctival lymphatic/blood vessels were a significant barrier whereas choroidal circulation contributed very little towards drug elimination. Molecular size may also affect drug clearance by conjunctival/episcleral mechanisms. For example, greater amounts of microparticles were retained compared to nanoparticles, and albumin exhibited a longer half-life than $^{22}$Na in the subconjunctival tissue [41]. Uveoscleral out-flow additionally may hinder transscleral diffusion as a fraction of the dose may pass along the convective current of aqueous humor and in due course be eliminated into the conjunctival vasculature. Detailed information on the effect of the physicochemical properties of the drug on clearance by choroidal/conjunctival vasculature and lymphatic system of the eye is lacking and needs to be addressed in the future.

4.3. Metabolic barriers

The importance of intestinal and hepatic metabolism in oral bioavailability is well appreciated. The presence of drug metabolizing enzymes have also been reported in the ocular tissues, with especially high expression levels being documented in the iris-ciliary, choroid and retinal pigmented epithelium, and to a lesser extent in the cornea, lens, aqueous humor and vitreous humor [71, 72]. Both phase-I and phase-II metabolic enzymes are expressed in the eye, with the cytochrome P450 family being the most predominant, as well as lysosomal enzymes [71]. The evidence of
metabolic activity in the blood-ocular-barrier components suggests a possible role of metabolism in the ocular drug bioavailability process [72].

Thus for effective transscleral drug delivery a thorough evaluation of the effect of disease states, physiological mechanisms and drug characteristics needs to be undertaken and built into the design stage.

5. Polymers used in ocular drug delivery

Polymers are an integral part of most drug delivery systems, including nanoparticles, liposomes, implants, hydrogels, micelles and ophthalmic solutions. Generally, two types of polymers are used, biodegradable and non-biodegradable. Choice of a particular polymer depends on numerous factors such as type of delivery system, physicochemical properties of the drug, rate of drug release, duration of drug release, target site, etc. Several polymers have been investigated in ophthalmic formulations including poly(lactic acid) (PLA), poly (lactide-co-glycolide) (PLGA), poly ethylene glycol (PEG), poloxamers, carbopol, chitosan, hydroxy propyl methyl cellulose (HPMC), Eudragit®, collagen, poly (ortho esters), poly (vinyl alcohol) and poly(1-vinyl-2-pyrrolidinone) (PVP). Polymers offer numerous applications: they can be used to modulate drug release and can thus be used in controlled or sustained drug delivery designs; they can control formulation viscosity and can also be used to impart mucoadhesive properties.

However, the eye is a very sensitive organ and a thorough evaluation of the safety profile of the polymer prior to their incorporation into ophthalmic formulations is necessary. Ocular safety can be estimated utilizing cell culture models and through in vivo testing. Although a good number of polymers have been used for ophthalmic applications, few studies have examined ocular tolerance of potential polymers. A review of the ocular toxicity profile of different polymers is presented in table 1.

6. Transscleral drug delivery systems (TDDS)

Although the transscleral route is comparatively more effective, drug is eliminated rapidly from the site of administration necessitating repeated administration. Research efforts, in recent years, have concentrated on the development of formulations that can maximize ocular absorption as well as display prolonged retention and release profiles at the site of application. Strategies examined include the design and development of novel dosage forms such as nanoparticles, liposomes, emulsions and hydrogels. These formulations present multiple advantages including controlled and sustained release of the drug over a period of time. From the patients’ standpoint, the
Table 1. Review of ocular safety profile of different polymers used for drug delivery to the eye.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Polymer</th>
<th>Formulation</th>
<th>Type of study</th>
<th>Results</th>
<th>Inference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chitosan</td>
<td>Nanoparticles [73]</td>
<td>In vitro toxicity study</td>
<td>Exposure to different concentrations of chitosan nanoparticles did not show any significant differences in cell survival and viability following immediate or 24-hour recovery periods.</td>
<td>Chitosan nanoparticles were well-tolerated at the ocular surface of rabbits.</td>
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<td></td>
<td></td>
<td>Nanoparticles [74]</td>
<td>In vivo tolerance study</td>
<td>No signs of histological alterations and abnormal inflammatory cells in the cornea, conjunctiva, and eyelids were evident.</td>
<td>Chitosan nanoparticles were well tolerated by conjunctival cells.</td>
</tr>
<tr>
<td></td>
<td>Chitosan</td>
<td>Nanoparticles [75]</td>
<td>In vivo testing</td>
<td>Intravitreal injection induced immune response causing inflammation</td>
<td>Chitosan should probably not be injected into the eye, at least at these concentrations.</td>
</tr>
<tr>
<td>2</td>
<td>PLA Poly(lactic acid)</td>
<td>Disc [76]</td>
<td>Histopathological study</td>
<td>Following subconjunctival administration, no sign of inflammation or toxicity was observed.</td>
<td>Non toxic.</td>
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<td></td>
<td>PLA and PLGA</td>
<td>Nanoparticles [77]</td>
<td>In vitro toxicity</td>
<td>Blank nanoparticles of PLA and PLGA had no effect on cell number and cell viability.</td>
<td>PLA and PLGA are safe to use for retinal drug delivery.</td>
</tr>
<tr>
<td></td>
<td>PLA</td>
<td>Nanoparticles [78]</td>
<td>Immunohistochemistry following intravitreal injection</td>
<td>Inflammatory response was similar to that of control eye. Anatomical and tissue integrity were preserved.</td>
<td>PLA nanoparticles can be used.</td>
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<td></td>
<td>PLGA</td>
<td>Nanoparticles [79]</td>
<td>Ocular tolerance test (HET-CAM test)</td>
<td>Low and high viscosity PLGA nanoparticles exhibited no signs of ocular irritancy.</td>
<td>PLGA nanoparticles are suitable for ophthalmic administration</td>
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<td></td>
<td>PLGA</td>
<td>Microparticles [80]</td>
<td>Ocular tolerance</td>
<td>Microparticles did not produce any changes in retinal atrophy, blood ophthalmic pathology, and in collagen deposition.</td>
<td>Microparticles are well tolerated and safe to administer</td>
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<td>3</td>
<td>PCEP (poly[(cholesteryl oxocarboxyamide ethyl) methyl bis(ethylene) ammonium iodide]) and Magnetic nanoparticles (MNPs)</td>
<td>Nanoparticles [75]</td>
<td>In vivo study</td>
<td>Intravitreal and subretinal injection of PCEP did not produce any inflammation or changes in retinal pathology.</td>
<td>Safe to be injected into the eye</td>
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<td>4</td>
<td>Eudragit RS100® and RL100®</td>
<td>Nanosuspension [81]</td>
<td>Ocular tolerability test (Drake test)</td>
<td>Irritation or toxicity was not observed.</td>
<td>Well tolerated.</td>
</tr>
<tr>
<td>5</td>
<td>Eudragit RS100&lt;sup&gt;®&lt;/sup&gt; and RL100&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Nanosuspension [82]</td>
<td>Ocular tolerance test (Delayed test)</td>
<td>No signs of inflammation and negligible conjunctival and iris hyperemia were observed; conjunctival swelling and discharge were not observed. Eudragit RS100&lt;sup&gt;®&lt;/sup&gt; or RL100&lt;sup&gt;®&lt;/sup&gt; nanospheres are safe.</td>
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<td></td>
<td>PEO 900-Chitosan HCl, PEO 400, PEO 900</td>
<td>Ocular insert [83]</td>
<td>In vivo tolerance test</td>
<td>PEO 900 or PEO 900-Chitosan produced slight reddening of conjunctiva and eyelid rim whereas PEO 400 produced slight reddening of only conjunctiva. Can be used for ophthalmic applications.</td>
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<td></td>
<td>PEO 200, PEO 400, PEO 900, PEO 2000</td>
<td>Ocular insert [84]</td>
<td>In vivo tolerance test</td>
<td>PEO 400 or PEO 900 produced slight reddening of conjunctiva whereas PEO 200 or PEO 2000 exhibited no irritation. All the tested inserts can be safely used.</td>
<td></td>
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<tr>
<td>6</td>
<td>Poloxamer&lt;sup&gt;®&lt;/sup&gt; 1, P407/P188/HPMC 2, P407/P188/NEC</td>
<td>Gel formulation [85]</td>
<td>In vivo tolerance test</td>
<td>Significant difference in redness, lacrimal secretion, mucosal discharge, swelling of eye lid between the two formulations and the marketed product (ciprofloxacin eye drop) was not observed. Can be used for ophthalmic applications.</td>
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<td>P407 (Lurol F127)</td>
<td>Poloxamer solution [86]</td>
<td>In vivo toxicity study</td>
<td>Following peribulbar injection, poloxamer solution did not bring about inflammation and extracellular matrix activation than injection of sodium hyaluronate or a mixture of sodium hyaluronate and chondroitin sulphate, compounds known to be safe. Poloxamer was devoid of local toxicity and can be used for peribulbar injection.</td>
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<td></td>
<td>Poloxamer</td>
<td>Intraocular lens (IOL) [87]</td>
<td>In vivo study</td>
<td>Inflammatory response or toxicity was not observed in cornea, iris, vitreous or retina. Poloxamer can be safely used as an injectable IOL.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phoric F127</td>
<td>pAl triggered in situ gel [88]</td>
<td>Ocular irritation test (HET-CAM test)</td>
<td>No irritation</td>
<td>Non irritant</td>
</tr>
<tr>
<td>7</td>
<td>HPMC and sodium alginate</td>
<td>Gel [89]</td>
<td>Ocular tolerance (Unize test)</td>
<td>HPMC and Sodium alginate formulations produced no ocular irritation. Safe to use</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PNIPAAm-PEO-DA poly (N-isopropylacrylamide) (PNIPAAm), cross-linked with poly(ethylene glycol) diacrylate (PEG-DA)</td>
<td>Hydrogel [90]</td>
<td>In vitro cell culture testing using Human Umbilical vein endothelial cells-MTT assay</td>
<td>Washing of the hydrogel were used for the toxicity study. The rationale was that the washings may contain toxic, unpolymerized PNIPAam. First washing of the hydrogel was toxic; however subsequent washings produced no toxic effects. Formulation should be used after washing for 5 times.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Poly (ortho esters) (POE) III and IV</td>
<td>Polymer solution [91]</td>
<td>Ocular tolerance study</td>
<td>Following subconjunctival, intravitreal, and suprachoroidal injections, both POE III and IV were well tolerated. Can be used for ocular drug delivery.</td>
<td></td>
</tr>
</tbody>
</table>
ideal formulation should: be simple and easy to administer, reduce the dosing frequency, and exhibit reduced side effects. However, selection of the drug delivery system depends on factors such as the nature of the drug molecule (physicochemical properties), targeted tissue (retina, choroid, vitreous humor etc), type of release desired (immediate or sustained) and dose considerations. The following sections discuss the formulation approaches involving particulate and emulsion and lipid systems, evaluated for back-of-the eye delivery.

6.1. Colloidal carrier systems

In the last two decades colloidal carrier systems have been extensively studied with the objective of targeting a specific organ or to increase bioavailability or to protect the drug from the biological matrix. Only recently these colloidal carriers have been investigated for ophthalmic administration [92]. Studies have mainly focused on improving transcorneal absorption for the treatment of anterior chamber ocular diseases. Some researchers have also targeted these systems to the posterior segment of the eye through systemic or intravitreal administration [92]. Only a few investigations have evaluated the feasibility of employing these colloidal drug delivery systems (DDS) for transscleral drug delivery.

6.1.1. Microparticles/Nanoparticles

6.1.1.1. Small molecule delivery

Nanoparticles are submicron sized colloidal systems (size ranging from 10 to 1000 nm). Particles above 1 micron (1000 nm) are termed microparticles. There are different types of nanoparticles classified on the basis of the polymer/polymers used (biodegradable or non-biodegradable) or type of particles obtained (nanospheres or nanocapsules). In the following sections various particulate systems evaluated for back-of-the eye diseases and administered transsclerally will be discussed.

Kompella et al. [93] studied nano and microparticles for retinal delivery of budesonide through subconjunctival administration. These particles were prepared with polylactide (PLA), a biodegradable, biocompatible polymer, using the solvent evaporation technique. In vitro release studies revealed a sustained drug release profile with the cumulative amount of drug released being approximately 50% of the initial loading in 2 weeks for the nanoparticles, and 23% in 6 weeks for the microparticles. Thus, microparticles sustained drug release more efficiently than the nano system. Additionally, the nanoparticles exhibited a burst release to the extent of about
25% of the initial drug content whereas the microparticles did not. These particulate systems were subconjunctivally injected into one eye (ipsilateral) of Sprague Dawley (SD) rats and the drug release and disposition characteristics were determined by estimating the drug content in the ocular tissues at predetermined time points, post administration. Consistent with the in vitro release data, the authors observed that the microparticles displayed improved sustained release characteristics compared to the nanoparticles (Fig. 2). The authors also concluded that direct transscleral penetration is the dominant diffusional pathway into the vitreous, subsequent to subconjunctival injection. This was based on the observation that detectable levels of budesonide were observed in the vitreous humor and retina of the ipsilateral eye but not in that of the contralateral eye. These findings ruled out the passage of the drug into the general circulation and then diffusion into the ipsilateral eye ocular tissues.

Figure 2: Budesonide nano and microparticles sustained ocular tissue levels of budesonide after subconjunctival administration in rats. Budesonide was administered in the eye of rats, either in the form of a solution (50 or 75 µg to one eye; small and large open circles, respectively), nanoparticles (50 µg to one eye; small filled circle), or microparticles (75 µg to one eye; large filled circle), and drug levels were estimated in (A) retina, (B) vitreous, (C) cornea, and (D) lens. Data are expressed as the mean ± SD of results in four experiments. Data are shown for the ipsilateral eye. Drug levels were below detection limits in the contralateral eye. Also, budesonide levels were below detection limits on day 14 in the solution and nanoparticle groups. Reprinted with the permission of Association for Research in Vision and Ophthalmology (ARVO), reference [93].
In another study, Ayalasomayajula et al. observed that retinal delivery of celecoxib was several fold higher upon subconjunctival administration [9] and inhibited VEGF expression in diabetes induced rats [94]. In order to sustain the release of celecoxib over prolonged periods, the feasibility of using microparticles were evaluated [95]. Celecoxib microparticles were prepared using poly (lactide-co-glycolide) (PLGA 85:15), a biodegradable, biocompatible and FDA approved polymer, using emulsion/solvent evaporation technique. Microparticles containing 75 μg of celecoxib were injected subconjunctivally into one eye of diabetic or non-diabetic SD rats. Two corresponding groups of control rats received celecoxib solution. In normal rats, at the end of 14 days post dosing, drug levels in the retina, vitreous, lens and cornea were found to be 1, 0.4, 0.1, and 0.6 μM respectively, which are significantly higher than the IC$_{50}$ values for COX-2 inhibition (0.003-0.006 μM). In diabetic rats, celecoxib-PLGA microparticles demonstrated inhibition of diabetes induced oxidative stress which was evaluated by estimating the glutathione, thiobarbituric acid reactive substances, and 4-hydroxynonenal levels. Thus, celecoxib-PLGA microparticles with sustained release characteristics effectively reduced diabetes induced oxidative stress in the retina. The contralateral eye, across all groups, showed no celecoxib levels.

Oral administration of PKC412 in a phase-2 clinical trial significantly decreased retinal thickening, a complication associated with macular edema in diabetic retinopathy patients [96]. However, oral administration was associated with several side-effects. Local delivery was subsequently investigated using microspheres prepared using PLGA, with 25 and 50 % drug loading. The formulations were pericocularly injected in a diseased pig model wherein choroidal neovascularization (CNV) was induced by laser photocoagulation. Image analysis (Fig. 3) was used to measure the area of CNV at the rupture site on the Bruch’s membrane. Tissue and plasma PKC412 levels were also estimated. At the end of 10 days, post injection, PKC412 was detectable in the choroid, but not in the retina or vitreous with the 50 % drug loading formulation. After 20 days PKC412 levels were detectable in quite high levels in the choroid with very low levels being observed in the retina and vitreous humor. Importantly, these levels effectively suppressed the development of CNV in vivo. Microspheres with 25 % drug loading also exhibited vitreo-retinal drug levels after 20 days, post injection. However, as expected, the levels achieved were less than that observed with 50 % drug loading [97].

Transscleral permeability of vinblastine and doxorubicin from solution and nanoparticle/liposome formulations were evaluated by Kim and coworkers [42]. Sustained and controlled release of vinblastine and
Figure 3. Periocular injection of microspheres containing PKC412 suppressed CNV. (A) Empty microspheres (placebo) were seen as bulges under the conjunctiva (arrows) 10 days after injection. There was a similar appearance 10 days after periocular injection of microspheres containing 25% (B) or 50% (C) PKC412. Gross pathologic examinations showed large collections of microspheres (arrows) that were similar in eyes injected with empty microspheres (D) or microspheres containing 25% (E) or 50% (F) PKC412. The microspheres often occupied an entire quadrant of the outside of an eye and extended back to the optic nerve (arrowheads). (G) Ten days after rupture of Bruch’s membrane and periocular injection of empty microspheres, a large area of CNV (arrows) was seen at a rupture site in Bruch’s membrane. (H) Ten days after rupture of Bruch’s membrane and injection of microspheres containing 25% PKC412, there was very little CNV (arrows) at a rupture site. (I) Ten days after rupture of Bruch’s membrane and injection of microspheres containing 50% PKC412, there was very little CNV (arrows) at a rupture site. (J) Another rupture site from an eye injected with empty microspheres shows a large area of CNV (arrows), whereas other rupture sites in eyes injected with microspheres containing 25% (K) or 50% (L) showed very little CNV (arrows). Reprinted with the permission of Association for Research in Vision and Ophthalmology (ARVO), reference [97].
doxorubicin was attained by encapsulating them in PLGA based nanoparticles and liposomes. It was observed that after 24 hours, 68 %, 74 %, 29 %, and 1.9 % of the initial amount was transported across the sclera from the vincristine solution, doxorubicin solution, PLGA-doxorubicin nanoparticles and Doxil® (marketed doxorubicin liposomal formulation), respectively. Thus, the data suggests that these anticancer molecules have sufficient transscleral permeability characteristics, as evident from the rate of diffusion of the drug from solution formulations, and that sustained release can be achieved using nanoparticle/liposome formulations.

6.1.1.2. Macromolecule delivery

Carrasquillo et al. developed controlled release microparticles for transscleral delivery of the anti-VEGF aptamer, EYE001 [98]. This aptamer is intended for treating CNV and diabetic macular edema. The goal was to develop an alternative to intravitreal injection and to sustain the release for over a period of 6 weeks. PLGA was used to formulate the microspheres. Considering the susceptibility of EYE001, a nucleic acid, to oxidation in aqueous solutions, trehalose was included in the formulation and a completely non-aqueous oil-in-oil methodology was developed for the preparation of the microparticles. In vitro drug release studies revealed a low initial burst release followed by a continuous release over a period of more than 20 days. In vitro transscleral diffusion studies indicated that scleral hydration was sufficient to degrade the microspheres, as evident from scanning electron microscope (SEM) pictures, and the released drug diffused across the sclera into the receiver chamber.

6.1.2. Liposomes

The utility of liposomes for delivering drug molecule to the posterior segment of the eye has been evaluated by Hironaka et al. [99]. Liposomes were prepared using phospholipids (egg phosphatidylcholine (EPC) or L-α-distearoyl phosphatidylcholine (DSPC)), dicetyl phosphate (DCP) and cholesterol and coumarin-6 was used as a model drug. Submicron-sized liposomes (ssLip) were obtained by passing multilamellar vesicles (MLV) through an extruder. Liposomes thus obtained, were topically administered to male adult ddY (Deutschland, Denken, and Yoken) mice. Fluorescence emission patterns obtained from the ocular tissues suggested that coumarin-6 reached the retina, when administered in this manner. Rigid ssLip was observed to be superior to MLV’s and DSPC based ssLip’s were more effective than those containing EPC. Epifluorescence microscopy of the entire eye indicated that the pathway to the retina, for the liposomes tested,
primarily involved non-corneal routes; possibly through the conjunctival membrane.

6.1.3. Disposition of non-biodegradable particulate systems from perioculr space

It is understood that microparticles are more efficient at sustaining subconjunctivally administered drug release than nanoparticles. Moreover, it is also known that biodegradable particulate systems, as the name suggests, are cleared by physiological mechanisms. To understand the disposition of non-biodegradable particulate systems, following subconjunctival administration, with respect to their size and surface properties, Amrite et al. [100] studied the disposition of fluorescent polystyrene particles, of various particle sizes (20, 200 nm and 2 μm) and surface properties (carboxylate modified, negatively charged), in SD rats. In general, periocularly administered particles were cleared from the site of administration either by transscleral penetration into the deeper ocular tissues or by entering into the systemic circulation through the ocular vasculature or were retained at the site of administration until cleared by the local lymphatic system. Significant levels of the nano- or microparticles were not observed in the retina, vitreous, lens or cornea. However, the 20 nm nanoparticles produced detectable levels in the sclera-choroid. Furthermore, with the larger particles (200 nm and 2 μm), nearly the entire dose administered was recovered from the site of administration at the end of 60 days. These findings thus illustrate that those particles with diameters >200 nm are suitable for sustained delivery purposes. Surface properties and hydrophobicity did not exhibit any effect on the disposition of the 200 nm and 2 μm particles, probably because the particle dimensions are above the cut-off value for elimination through the periocular tissue. However, with the 20 nm particles, retention of hydrophobic particles was almost 85 % greater than the retention of hydrophilic particles. Further studies [101] with 20 nm particles revealed that periocular circulation (blood and lymphatics) plays a vital role in clearance of 20 nm particles and permeation of these nanoparticles across the sclera-choroid-RPE was insignificant.

6.2. Miscellaneous

6.2.1. Cyclodextrins

Cyclodextrins can increase aqueous solubility of lipophilic compounds and may thus promote diffusion of such agents across the aqueous tear film to the surface of the corneal epithelium. Loftsson et al. [102] investigated the
delivery of dexamethasone to the retina following topical application. Two types of cyclodextrins, randomly methylated beta cyclodextrin (RMβCD) and gamma-cyclodextrin (γCD), were used for the preparation of aqueous dexamethasone dispersions (1.5 % drug content). It was observed that formulations containing γCD were more efficient, compared to those formulated with RMβCD, in delivering drug to the retina: the retinal dexamethasone concentration was 28 and 9 ng/g of tissue with γCD and RMβCD, respectively. Additionally, vitreal drug concentrations also revealed a similar trend, 25 and 16 ng/mL for γCD and RMβCD based formulations, respectively. Furthermore, plasma drug levels were lower with γCD compared to RMβCD. Based on the results obtained, the authors hypothesized that γCD-drug particle complex was retained on the ocular surface longer, resulting in prolonged saturation of the tear film, thus leading to higher drug concentrations in the retina and vitreous.

6.2.2. Fibrin sealant

Collaboration between ophthalmologists and biopharmaceutical scientists led to the development of the fibrin sealant. Generally, fibrin sealants are used as a surgical adhesive when stoppage of bleeding by regular surgical techniques is ineffective. It is composed of both human and bovine components, and consists of human sealer protein concentrate (human fibrinogen and factor XIII), bovine fibrinolysis inhibitor, human thrombin, and calcium chloride. Now-a-days fibrin sealant is being explored as a biodegradable, semisolid transscleral drug delivery system. The key benefits of this approach include: 1) the components of the fibrin sealant are in a liquid state and, thus, a clot can be produced at the desired site, the scleral surface, on injection 2) it is possible to incorporate anhydrous forms of a drug molecule as a dispersion in the sealant, 3) immunogenic reactions are less pronounced because it is made up of proteins of human origin, and 4) it provides controlled release characteristics with its fibrinolysis based degradation mechanism [103]. Current literature suggests that delivery of carboplatin, used in the treatment of retinoblastoma, can be sustained using fibrin sealant technology [104-106]. Simpson et al. demonstrated that choroidal and vitreal concentrations of the drug, using these systems, were consistently higher than that achieved with a drug solution in balanced salt solution (BSS) [106]. Subsequently, Van Quill et al. evaluated the efficacy of subconjunctival carboplatin in a randomized, controlled trial in transgenic mice with placebo, and low dose or high dose carboplatin, in a fibrin sealant. The authors reported that even with the low dose carboplatin, complete intraocular tumor regression was achieved and was comparable in efficacy to
the high dose study, the latter being associated with severe toxicity. Sustained release was also observed for dexamethasone and methotrexate from the transscleral fibrin sealant delivery systems [107].

6.2.3. Unidirectional episcleral exoplants

Parallel elimination pathways, as described in previous sections, associated with transscleral drug delivery have a profound effect on the overall vitreal bioavailability of drug molecules. If the drug loss is prevented or reduced at the site of administration, ocular bioavailability may be increased. Towards this purpose, a new drug delivery system was designed by Pontes de Carvalho et al. [108] in which drug is loaded in an impermeable reservoir that allows drug diffusion only towards the sclera (Fig. 4). The concept was tested using fluorescein as a model drug and two prototype exoplants, one designed for use with solid formulations and the other, a flexible silicone refillable exoplant, suitable for liquids and suspensions. As the name suggests, drug replenishment is possible with the second exoplant. The results demonstrate that when the exoplant was sutured to form a firm seal with sclera, an early peak in the retina and posterior vitreous was observed, with increasing concentrations of fluorescein in the anterior part at later stages. However, when the exoplant was placed on the sclera but a tight seal was not formed, two early peaks were observed, one in the retina and the other in the anterior chamber. An early peak in the anterior chamber, in the

Figure 4. Schematic of episcleral exoplants. (A) The appearance of the rigid polyethylene episcleral exoplant sutured to the globe. (B) The refillable silicone episcleral exoplant is flexible and forms a seal with the globe without tight suturing to the globe. Reprinted with the permission of Association for Research in Vision and Ophthalmology (ARVO), reference [108].
latter case, was due to diffusion of the drug from the periocular space into the cornea and subsequent absorption. A similar phenomenon was also observed following periocular injection of fluorescein solution. The flexible silicone refillable exoplant produced markedly higher drug levels in the posterior segment of the eye compared to a simple periocular injection. The study demonstrates that by decreasing parallel elimination pathways in the periocular space it is feasible to increase the vitreal bioavailability of therapeutic agents administered by the transscleral route.

7. Pharmacokinetic modeling of transscleral drug delivery

This section briefly discusses the ocular pharmacokinetic modeling aspects of a drug molecule following transscleral administration.

7.1. Pharmacokinetic model for transscleral drug delivery

Lee and Robinson [109] developed a simple pharmacokinetic model as depicted in Figure 5. In this model three rate constants are used to mathematically model drug levels in the vitreous humor: \( k_{10} \) is a rate constant associated with drug loss from the subconjunctival space; \( k_{12} \) a rate constant representing drug absorption/penetration from the subconjunctival space into the vitreous humor; and \( k_{20} \) represents the elimination rate constant from the vitreous humor.

The authors proposed that vitreal bioavailability (BAv) of a drug following periocular administration can be calculated, using equation 1, by dividing the absorption rate constant through the direct penetration pathway (\( k_{12} \)) with that of overall rate constant for drug loss from the periocular space (\( k_{12} + k_{10} \)) [110].

![Figure 5](image-url) A simplified pharmacokinetic model following subconjunctival administration of a drug, for absorption into the vitreous humor by direct penetration pathway. Abbreviations: \( k_{10} \), rate constant of drug elimination from subconjunctival space; \( k_{12} \), rate constant of drug absorption into vitreous humor; \( k_{20} \), rate constant of drug elimination from vitreous humor.
In general, for most drugs administered through the periocular route, transscleral diffusion rate is much lower than the rate of drug loss from periocular site ($k_{12} \ll k_{10}$), resulting in lower vitreal bioavailability. The existence of a parallel elimination pathway ($k_{10}$) at the periocular site of administration has a profound effect on the total BA$_v$ [111]. Moreover, parallel elimination pathways also affect peak time ($T_p$) and peak concentration ($C_{max}$) of a drug in the vitreous humor. On the other hand, $T_p$ is not affected much by altering $k_{12}$. However, an increase in $k_{12}$ can increase the $C_{max}$ of a compound. The $k_{20}$ plays a major role in sustaining the vitreal drug level for longer duration of time only. In short, the authors suggest that if a formulator wants to alter both $C_{max}$ and $T_p$, varying $k_{10}$ will be an ideal choice; alternatively, if only $C_{max}$ need to be changed, then varying $k_{12}$ will be a good choice [111]. Thus, vitreal bioavailability can be improved either by decreasing $k_{10}$ or by increasing $k_{12}$ through formulation strategies or by designing a drug with appropriate physicochemical properties. For example, Kansara et al. demonstrated that transscleral permeability of the dipeptide monoester prodrugs of ganciclovir was significantly higher than that of the parent drug, ganciclovir, [112] probably due to changes in the lipophilicity and/or uptake of prodrugs by the oligopeptide transporter expressed on the RPE. Furthermore, Allergan Inc. filed a patent application [113] which also describes sustained delivery of drug molecules to the posterior segment of the eye through prodrug derivatization. The inventors observed that ester prodrugs when administered through the subconjunctival or periocular routes, deliver the active drug to the vitreous or retina more efficiently. Additionally, the inventors claim that this type of delivery is good for drugs with low therapeutic indices.

Controlled drug delivery systems can successfully minimize the variations in peak and trough concentrations observed with subconjunctival administration of simple solutions [114]. In these systems, pharmacokinetic profiles will be dictated by drug release rate constant ($k_r$) from the formulation. The drug release can be either zero-order ($k_{0}$) or first-order ($k_{1}$) depending on the type of formulation and methodology. According to Lee and Robinson, for zero-order release systems, in general, drug release rates greater than 1 µg/h will give rise to vitreal concentrations greater than 1 ng/mL, except for drugs with low transscleral BA and/or rapid elimination. Thus, if therapeutic efficacy requires greater than 1 µg/mL, very high doses need to be administered to achieve the necessary release rates. In this scenario subconjunctival injection is not a feasible mode of delivery, unless the magnitude of $k_{12}$ is increased or $k_{20}$ is decreased to improve BA. Drug
delivery systems with first-order release rates, lie between simple subconjunctival injections and zero-order delivery systems with respect to vitreal BA. The peak concentration obtained, with a first order release system, will be lower than that obtained with simple subconjunctival injections and therapeutic levels will be maintained for short durations only. Thus, DDS with a zero-order release is the ideal choice for sustaining ocular drug delivery. Nevertheless, it is also possible to sustain the drug delivery with first-order release systems, provided two parameters (dose and $k_1$) are optimized through formulation approaches; increasing the dose can sustain the delivery, however peak concentration will also be high for obvious reasons and decreasing the $k_1$ can also sustain the delivery [114].

Drug distribution into various ocular tissues and its elimination following transscleral drug delivery depends, to a large extent, on the partition characteristics of the drug into the ocular tissues. In a recent study [115], range of beta-blockers differing in lipophilicity were tested for their partitioning into various Ocular tissues associated with transscleral drug delivery; choroid-RPE, sclera, retina, trabecular meshwork and optic nerve. Interestingly, drug partitioning into choroid-RPE, iris-ciliary body, sclera and cornea increased with an increase in drug lipophilicity, whereas tissues like retina, vitreous, and lens exhibited an opposite trend. Among these tissues, partitioning into choroid-RPE was much higher than all other tissues (choroid-RPE > trabecular meshwork > retina > sclera ~ optic nerve). Thus it can be concluded that drugs which bind limitedly to choroid-RPE might exhibit higher transscleral drug delivery to the innermost tissues of posterior segment of the eye; retina and vitreous. Another key finding of the study, from an experimental standpoint, is that in vitro bovine tissue/PBS partition coefficients correlated very well with in vivo tissue/vitreous drug distribution ratios. Once the drug diffuses into the vitreous compartment, it can get further distributed into the peripheral compartment(s) depending on its physicochemical properties. This could give rise to multi-compartment pharmacokinetic models. Lee and Robinson demonstrated that prednisolone exhibits a two compartment pharmacokinetic model following subconjunctival delivery [111].

For new molecular entities, preclinical pharmacokinetic parameters are, generally, determined in animal models like rats and rabbits. Amrite et al. [116] observed that elimination rate constants from the perilocular space and the cornea, for two different lipophilic molecules, are in the similar order of magnitude between rats and rabbits. However, it is cautioned that rate constant was lower in rabbits, which may be because of differences in species or drug characteristics and need to be considered carefully for each molecule.
7.2. Pharmacokinetic simulation models

Ranta and Urtti designed a pharmacokinetic simulation model for transscleral drug delivery based on the in vitro permeability data across various ocular tissues (sclera, choroid, RPE) [110]. The authors suggest that utilization of this model can provide some insights into the different rate limiting barriers to transscleral drug delivery and help predict drug’s pharmacokinetic behavior. The suitability of the model was demonstrated using previously reported in vitro permeability data of FITC-dextran.

The key features of the model include 1) use of in vitro permeability data, and 2) consideration of physiological factors associated with drug elimination like choroidal clearance and clearance from the vitreous humor. Like any other model it is also associated with a few limitations and disadvantages, such as a) only passive diffusion across the RPE is considered, b) diffusion across the neural retina is not considered, c) difficulty in measuring drug loss through the choroidal circulation, d) drug loss at the episcleral surface and conjunctiva is not considered and e) predicted pharmacokinetic parameters should be interpreted carefully as values are not obtained from real, in vivo, conditions.

In the direct transscleral penetration pathway choroidal circulation can act as a sink for permeating drug molecules [67] and several molecules may display asymmetric transport across the RPE because of the involvement of active transport processes. Balachandran et al. [66] developed a computational model incorporating these parameters. Additionally, metabolism and efflux in the ocular tissues were also considered.

The readers are encouraged to refer to the original articles [66, 110] for further information on these mathematical simulation models.

8. Conclusion

The transscleral route is suitable for delivering a wide range of therapeutic agents, from small molecules to large proteins, for the treatment of back-of-the-diseases, by virtue of its easy accessibility, large surface area and relatively high permeability to a range of drug molecules. Designing colloidal DDS’s for transscleral application is a potential approach for achieving sustained and controlled release of the drug at the target site; however, it probably does not present an unique solution to the challenges associated with back-of-the eye drug delivery. The unidirectional DDS provides a novel delivery platform which in conjunction with the colloidal delivery systems may prove to be a very effective therapeutically. However, further studies are necessary to obtain a detailed understanding of the factors
affecting transscleral drug delivery as well to identify potential toxicity issues with the formulation components.

References

Transscleral drug delivery to the posterior segment of the eye