The suprachoroidal space as a route of administration to the posterior segment of the eye

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Abstract

The suprachoroidal space (SCS) is a potential space between the sclera and choroid that traverses the circumference of the posterior segment of the eye. The SCS is an attractive site for drug delivery because it targets the choroid, retinal pigment epithelium and retina with high bioavailability, while maintaining low levels elsewhere in the eye. Indeed, phase III clinical trials are investigating the safety and efficacy of SCS drug delivery. Here, we review the anatomy and physiology of the SCS; methods to access the SCS; kinetics of SCS drug delivery; strategies to target within the SCS; current and potential clinical indications; and the safety and efficacy of this approach in preclinical animal studies and clinical trials.

Graphical Abstract
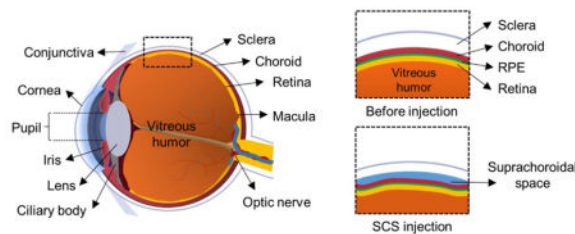
Keywords

microneedle; suprachoroidal space; ocular drug delivery; ophthalmic targeting; posterior segment of the eye; uveitis; macular edema

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1 The need for novel routes of administration to the posterior segment

Ocular pathology and disease can result in visual impairment and blindness, and consequently, significant loss in quality of life[1–4]. In particular, posterior segment diseases, such as age-related macular degeneration (AMD), diabetic retinopathy (DR), noninfectious uveitis, or central serous chorioretinopathy, can result in permanent vision loss once retinal architecture and physiology are disrupted[5]. The effectiveness of existing and new drugs is limited by the delivery of these drugs to the site of disease in a spatially and temporally controlled manner due to the eye's small size and unique barriers[6–8].

Traditional routes of delivery, namely topical eye drops and intravitreal injections, are the current gold standards used for treating ophthalmic disease. Topical eye drops result in low bioavailability (1–7%) within the anterior chamber of human eyes, and negligible penetration past the anterior chamber[9, 10]. Thus, topical eye drops have limited applications in the management of posterior segment diseases in humans. Intravitreal injections of corticosteroids and monoclonal antibodies against vascular endothelial growth factor (VEGF) have been used to treat retinal diseases with great effect and have revolutionized the treatment of posterior segment diseases[6, 7, 11–14]. Such a procedure can be performed in the outpatient clinic setting by a trained ophthalmologist under topical or local anesthesia. The vitreous humor acts as a natural depot, slowly releasing drug over ~1 month, depending on formulation[15, 16]. However, the drug diffuses isotropically through the vitreous and can thus diffuse towards non-target regions of the eye (e.g., lens and ciliary body), resulting in side effects[17–21]. An intact blood-retinal barrier can also impede the transport of drugs from the vitreous to the choroid and retinal pigment epithelium [8, 22]. In summary, traditional ophthalmic routes of administration are not able to target specific tissues within the eye, resulting in low bioavailability at the diseased tissue(s) and/or possible side effects due to drug affecting non-target tissues.

1.1 The suprachoroidal space as a novel route of administration

The suprachoroidal space (SCS) is a potential space found between the sclera and choroid (Figure 1). Under typical physiological conditions, the SCS is mostly collapsed due to the intraocular pressure (IOP) and fibers that attach the sclera to the choroid[23, 24]. The SCS has a nominal thickness of 35 μm, so that the choroid can slide against the sclera during accommodation[24, 25]. The SCS plays a role in maintaining IOP via the uveoscleral outflow, which is an alternative drainage route for aqueous humor[26]. Suprachoroidal hemorrhage is an urgent ophthalmic indication, where the choroid bleeds into the SCS. Patients with suprachoroidal hemorrhage report significant pain and can have vision loss. Surgery may be necessary to drain the hematoma and re-appose the sclera and choroid. Therefore, any procedures that access the SCS should avoid causing hemorrhage.

Due to its proximity to the choroid, the SCS is an attractive site of drug delivery for posterior segment diseases because high bioavailability within the choroid and potentially retina can be achieved[27, 28]. Thus, a lower drug dose (aka, dose sparing) can be used to achieve similar efficacy compared with traditional routes of administration[29]. Furthermore, drug is compartmentalized in the SCS away from non-diseased tissues, which is expected to result in a more favorable side-effect profile[27, 28]. Because of these reasons, drug delivery via

the SCS has become an attractive alternative and/or adjunct that is under intense investigation. Most of the research in this field has occurred recently. In fact, of the 39 peer-reviewed research articles indexed on PubMed with the term 'suprachoroidal drug delivery', 6 were published in 2017 and 23 were published in 2013 – 2017.

2 Accessing the suprachoroidal space

A method or procedure to access the SCS in a safe, reliable, and efficient manner has been a major hurdle preventing widespread use of this route of administration until recently (Figure 2). In the preclinical setting, access has generally been via sclerotomy (i.e., cutting across the sclera); *ab interno* surgical approaches have also been used for surgical implantation of glaucoma filters. However, the only method that is currently FDA-cleared is a sclerotomy with micro-cannulation into the SCS (iScience catheter, Ellex Medical, Adelaide, Australia), although this method is not standard of care[30]. As with all surgical approaches, there are risks associated and the procedure must be performed in the operating room. Because an intravitreal injection is easier to perform and carries a relatively low risk, it has been the preferred method of posterior segment delivery. Ongoing clinical trials testing the safety and efficacy of microneedle injections into the SCS have demonstrated that this procedure is reliable and efficient, and can be performed in the outpatient ophthalmologist office under local anesthesia.

2.1 Surgical incision

Drug delivery to the SCS has been achieved by dissecting through the sclera under general or monitored anesthesia[31–37]. Access to the SCS can be achieved via a full-thickness scleral incision, generally with a scalpel, performed in the operating room[28, 31–34, 38–43]. Identification of the scleral-choroidal junction (where the SCS is found) requires slow and delicate dissection so as not to inadvertently cut through the choroid and retina. The retinal pigment epithelium and pigmented choroid serve as a readily identifiable plane to dissect to. Once the sclerotomy is completed, a blunt-tipped catheter can be used to tunnel through the SCS towards the posterior pole[28, 32, 33, 37, 40, 41]. A catheter with a flashing diode has been used to visualize the advancement of the catheter under a microsurgical scope[28, 33]. After infusion, sutures may or may not be used to seal the sclera. The benefits of accessing the SCS via incision and catheterization is that the site of drug delivery can be visualized and chosen by the ophthalmologist. For example, this might be beneficial when targeting chemotherapies to the SCS underlying ocular tumors[44].

Monolithic implants have been placed into the SCS after surgical incision through the sclera. These have been used for a variety of indications, including drug delivery[34, 43, 45–47], glaucoma[48], retinal degeneration[49, 50], and retinal detachments[51–55].

2.2 Ab interno

The Cypass (Transcend[56]) and iStent (Glaukos[57, 58]) micro-stent medical devices are used for lowering IOP in glaucoma refractory to medical therapy. They are surgically implanted within the SCS during cataract surgery using an *ab interno* approach. During cataract surgery, the micro-stent is guided into the anterior chamber through the keratotomy

incision (i.e., corneal incision) and pierced through the scleral spur opposite the keratotomy. Once in position, the device serves as a conduit to enable fluid egress from the anterior chamber to the SCS, thereby enabling IOP reduction.

2.3 Injections

Some groups chose to use a hypodermic needle to directly inject into the SCS[36, 53, 59–63]. This can be a challenging procedure, since visualization of the scleral-choroidal plane is not possible with this method, and instead tactile cues must be used to indicate when the sclera has been penetrated. When used to evacuate suprachoroidal hemorrhage, there is more leeway in targeting an ideal depth because the SCS is expanded with blood[60]. However, when targeting the typically collapsed SCS, this technique is highly dependent on user experience, as a 30 gauge hypodermic needle (~300 μm outer diameter, bevel length > 1 mm) is directed through the ~500 μm thick sclera[64]. Furthermore, demonstrating safety of this method in the clinical setting would be complicated given the sharp learning curve and variability among users. Another issue is targeted drug delivery within the SCS, since the injected material should be targeted towards diseased regions; strategies to guide drugs to specific regions of the SCS are under investigation.

2.3.1 Microneedles—Microneedles have been developed and used to deposit drug into the SCS in a simple and reliable manner[65, 66] (Figure 3). A microneedle is a hollow-bore needle with a length matched to the thickness of the sclera and conjunctiva. The length is chosen so the microneedle is physically unable to penetrate deeper than the SCS (i.e., through the choroid and retina) and perform an inadvertent intravitreal injection. Fluid injected into this space spreads circumferentially within the SCS, bathing the choroid with drug. Furthermore, the same procedure used for intravitreal injection can be used with a microneedle for SCS injection, and can thus be performed in the outpatient clinic setting by ophthalmologists with patients under local anesthesia. To accurately control the insertion depth, the microneedle is positioned perpendicular to the scleral surface and the hard stop at the hub at the microneedles' base contacts the sclera/conjunctiva. Reflux out the injection site is possible, so the microneedle is often kept in position for ~1 min to minimize reflux. Injection success was found to be dependent on needle length, needle gauge, infusion pressure, and particle size, and did not depend on intraocular pressure[65]. Parameters that affect the force of microneedle penetration through the sclera and into the SCS have been studied, and can be easily administered by hand[67].

3 Pharmacokinetics within the suprachoroidal space

3.1 Distribution within ocular layers

Immediately after injection into the SCS, higher levels of small molecules and macromolecules were found in the choroidal, retinal pigment epithelium (RPE), and retinal tissues, compared with intravitreal injections[27, 28, 33, 36, 37, 59, 61, 62, 65, 66, 68, 69]. For example, fluorescein was selectively localized to the chorioretina 25–200 times more with than an intravitreal injection[27, 66]. Immediately post-injection of 3mg of bevacizumab, 0.2 μg/mg-tissue and 1.6 μg/mg-tissue of bevacizumab were detected in the choroid after intravitreal and suprachoroidal delivery, respectively[28]. Suprachoroidal

injection of bevacizumab resulted in significantly lower drug levels in the aqueous humor and vitreous humor [28]. The concentration of ketorolac detected in the chorioretina was 208 μg/g after intravitreal injection at 30 min and 57 μg/g after suprachoroidal injection at 1 h[37]. Stem cells injected into the SCS using a novel injector were localized to the extravascular choroid [35, 63, 70]. Furthermore, anterior segment tissues, including lens, aqueous humor, and cornea, were largely spared from drug [27, 28, 36, 61, 66]. However, drug was cleared significantly faster with SCS delivery than intravitreal or subconjunctival injections, with small molecules being cleared within a few hours and macromolecules within one day[28, 36, 38]. Particles as small as 20 nm, however were not cleared from the SCS [66, 71]. For this reason, long-acting formulations are needed to enable extended drug delivery in the SCS after a single injection [28, 66, 71–73]. In contrast, the vitreous humor can serve as a depot that slowly releases drug – including small molecules and macromolecules – to the retina and adjacent choroid[15, 16, 28, 74].

3.2 Circumferential distribution

Though fluid delivered into the SCS distributes circumferentially around the eye in the SCS, it does not typically cover the entire space[66, 68, 75]. Similarly, most ocular diseases do not affect the eye uniformly (e.g., AMD affects the macula while sparing the peripheral retina[76–78], while retinitis pigmentosa affects the peripheral retina while sparing the macula[79]). Therefore, targeting to specific regions of the SCS is of interest. Targeting within the SCS can be achieved via the catheterization approach or via formulations and other methods that control spread within the SCS during and after injection.

When particles were injected into the SCS using a microneedle, their flow within the space was limited by the scleral spur and optic nerve[25, 65, 66]. Additional anatomical barriers (the long posterior ciliary arteries in rabbits *ex vivo* and *in vivo* and the short posterior ciliary arteries in human cadaver eyes) have also been seen to prevent circumferential particle spread within the SCS[80]. Particles injected in close proximity to these vessels did not spread isotropically like particles injected far from these anatomical features.

Since the SCS is distensible, it is important to determine how injected fluid distributes within the SCS: by increasing circumferential area, by increasing the cross-sectional thickness, or a combination of the two[71, 81]. Multiple studies have shown that increasing injection volume resulted in increasing coverage area[65, 66, 68, 71, 75, 81]. However, it was difficult to cover 100%, likely due to anatomical barriers[80]. Maximal SCS thickness was found to depend on injection volumes, with thickness ranging from 1.7 to 2.8 mm[31]. While the thickness generally increased with injection volume, there did not appear to be a linear trend, especially with IOP at physiological levels[31]. Other studies found that increasing injection volumes resulted in increasing SCS cross-sectional area under optical coherence tomography[68] and, separately, that the median SCS thickness was constant (~160 μm)with injection volumes ranging from 25 μL to 150 μL[71]. The SCS thickness could, however, be further increased by up to 2.8 mm at the site of injection by injecting highly viscous formulations into the SCS[71]. These two findings suggest that SCS thickness is determined by a force balance between the viscous forces of the injected formulation that limit spreading over larger areas in the SCS and the biomechanical elastic

forces of the tissue and the SCS fibrils that run between the sclera and choroid that inhibit expansion of SCS thickness [71].

Ultrasound contrast agent injected into the SCS showed a distribution that was near the scleral spur (i.e., the most anterior portion of the SCS) with the cornea facing up, probably due to buoyancy of the low-density particles[31]. High-density particles injected in the SCS could similarly use gravity to control particle distribution[82]. The dense particles sank via decreased buoyancy towards the back of the eye if the eye was oriented upright with respect to gravity, thereby targeting the most-posterior structures like macula.

Other studies have shown that formulations – notably including polymers that impart high viscosity – can influence distribution of particles in the SCS not only during injection but subsequently too[75]. For example, carboxymethyl cellulose localized the injected particles near the site of injection due in part to crosslinking of the polymers to create a gel [29, 75]. In contrast, hyaluronic acid increased viscosity such that spreading during injection was inhibited, but over the course of hours to days after injection, the presence of hyaluronic acid enabled injected particles to spread to cover up to 100% of the SCS. Polymeric formulations (such as hyaluronic acid) are hypothesized to spread well after injections since they exert an osmotic pressure that seeks to imbibe fluid, resulting in expansion of the formulation, and may also coat particles and/or tissue to prevent non-specific binding. By tracking the distribution of particles and fluid formulations simultaneously, the injected fluid traveled further into the SCS than the injected particles when using low-viscosity formulations, suggesting some degree of particle entrapment with the SCS; with high-viscosity formulations, the discrepancy between the travel distance of the particle and polymeric formulation was decreased [81]. These findings suggest that these viscous formulations increased transit time in the SCS, and reduced particle-tissue interactions[81].

3.3 Clearance

3.3.1 Clearance kinetics from the SCS—When comparing the pharmacokinetics and distribution of molecules in the SCS against intravitreal injections, higher levels of injected molecules have been found in the chorioretina with significantly faster clearance after SCS injection. SCS collapse, which can be used as a proxy for clearance of injected liquid (i.e., water) from the SCS was found to reach baseline levels within 40 – 60 min[68, 83].

Considering clearance of molecules, higher levels of bevacizumab were found in the chorioretina 12 h after SCS injection compared with intravitreal injection[28]. However, at 7 days, bevacizumab was undetectable in the SCS group, but remained relatively high in the intravitreal group. Another study reported a clearance half-life of 3.6 – 7.9 h for various macromolecules injected into the SCS[65, 66]. Sodium fluorescein concentration in the chorioretina was found to be 25-fold higher after SCS injection compared with intravitreal injection; however, 2 h after injection, fluorescein levels in the chorioretina were higher in the intravitreal injection group than in the SCS group[62]. Similarly, the elimination half-life of another small molecules, ketorolac, was longer after intravitreal injection than SCS delivery (3.1 h vs. 1.2 h)[36] and, surprisingly, corresponded to a lower C_{max} in the chorioretina for the SCS group than the intravitreal group.

Increasing molecular weight up to 500 kDa had only a minor effect on SCS clearance rate[28, 66, 83]. Molecules up to 500 kDa were cleared from the eye within 2 days, but very large macromolecules (2 MDa) had significantly slower clearance than the 500 kDa macromolecules, taking up to 20 days to fully clear[83].

Polystyrene microparticles with diameters as small as 20 nm delivered into the SCS could be found at least 4 months post-injection[65, 66, 75]. Because macromolecules are not rigid, they may be able to adopt a conformation that can exit the eye (e.g., via blood capillaries). On the other hand, polystyrene microspheres are rigid and cannot change conformation and thereby cannot fit into pathways that exit the eye.

3.3.2 Clearance route from the SCS—The route of clearance from the SCS is also a topic of interest. After intravitreal injection, xenon and radioactive water were cleared from the eye via choroidal blood flow[84, 85], which has been proposed as the clearance pathway after SCS injection too[28, 61]. Consistent with this hypothesis, fluorescein was cleared from the SCS significantly faster with choroidal perfusion in the living eye than without in a *postmortem* porcine model[38]. In the context of studies elucidating the uveoscleral outflow pathway, microspheres injected into the anterior chamber were found trapped in the SCS especially where blood vessels penetrated through the sclera (aka., perivascular drainage routes)[86, 87], suggesting this as another pathway for SCS clearance. By systematically studying the clearance routes of fluorescein from the SCS, another study identified three regimes of clearance: (i) initial leakage of fluorescein from the injection site and perivascular leakage sites, which occurred on a timescale of minutes; (ii) pressure-driven trans-scleral movement of fluorescein on a timescale of tens of minutes, (iii) diffusion into the choroid and subsequent intravascular clearance on a timescale of hours[83] (Figure 4). These results were corroborated with a two-dimensional mathematical model of the SCS and surrounding tissues[83].

4 Pharmacodynamics

4.1 Distribution within cell layers

SCS delivery can result in high bioavailability in the sclera, choroid, and RPE[28, 32, 36, 59, 61, 66, 68–70, 88, 89]. For example, a small molecule HIF-1 inhibitor injected into the SCS of rats distributed throughout the choroid and retina, and prevented choroidal neovascularization in an animal model with selective destruction of Bruch's membrane[69]. In another study, gene transfection was noted in the choroid and RPE after SCS delivery of genetically-engineered adeno-associated virus[32] and nonviral plasmids[88]. And stem cells injected into the SCS were distributed to up to 80% of the SCS, present for at least 10 weeks within the SCS, and were well tolerated without immunosuppression [70]. There is less information about bioavailability within the retina, though steroids injected into the SCS have been shown to resolve macular edema[46, 47, 73, 90]. The cornea, anterior chamber, and lens receive negligible concentrations of drug. Furthermore, dose sparing of drugs that have their mechanism of action at the ciliary body has been reported when using formulations that target the anterior SCS adjacent to the ciliary body[29, 72]. This pattern of distribution is very different than intravitreal injections[28, 36, 66] or topical eye drops[9].

4.2 Drug targets

4.2.1 Choroid—The choroid is a prime drug target for SCS delivery, since the choroid lines the SCS inner surface. Possible diseases of interest that affect the choroid include noninfectious uveitis, dry forms of AMD, choroideremia, uveal melanoma, and central serous chorioretinopathy. The therapeutic effects of corticosteroids[33, 45, 59, 73, 90], small molecules [29, 36, 46, 47, 69, 72], monoclonal antibodies[33, 62], and cells[35, 63] injected into the SCS have been tested in preclinical and clinical trials. Indeed, phase I/II clinical trial results have been promising[73]. Nine participants with noninfectious uveitis were treated with a microneedle injection of triamcinolone into the SCS, and good efficacy and safety were reported. Thirty-eight adverse events were reported, most commonly pain at time of injection. It is worth noting that injection of a corticosteroid like triamcinolone acetonide is expected to reduce inflammatory side effects and thereby affect the safety profile. Phase III clinical trials are underway to test the efficacy of a microneedle injection of triamcinolone acetonide into the SCS to treat noninfectious uveitis (NCT 03097315) and macular edema associated with retinal vein occlusion (NCT 02980874).

4.2.2 Ciliary body—Disease progression of primary open-angle glaucoma can be slowed with IOP-lowering medications and surgeries[9]. The SCS is bordered anteriorly by the ciliary body, which produces aqueous humor and inflates the eye. Furthermore, the SCS plays a role in uveoscleral outflow, one of the routes of aqueous humor drainage from the eye. Two preclinical studies have demonstrated that SCS delivery of ocular hypotensive agents results in IOP reduction[29, 72], as a potential treatment for glaucoma. These studies also showed dose-sparing with SCS injection compared with eye drops. Micro-stents penetrated through the scleral spur to generate a fluid conduit from the anterior chamber into the SCS have been shown to reduce IOP in glaucoma patients[48, 57, 91].

4.2.3 Retinal pigment epithelium—The RPE is a monolayer of epithelium with tight junctions that maintains the outer blood retinal barrier. Bruch's membrane serves as the basement membrane for the RPE and the underlying choropcapillaris. Preclinical pharmacokinetic studies have demonstrated that high bioavailability is possible at the RPE, compared with other routes of administration[28, 32, 88]. Diseases of interest that are associated with RPE pathology include wet forms of AMD, and central serous chorioretinopathy. Though the pathogenesis of choroidal neovascularization is unknown, dysfunction of the RPE, Bruch's membrane, and choriocapillaris have been implicated. No studies have yet used SCS delivery for therapeutic effect on the RPE. Studies have shown that choroidal neovascularization is more effectively treated with intravitreal injections of a receptor tyrosine kinase inhibitor than SCS injections, although the authors noted incomplete delivery with the SCS injection[89].

4.2.4 Retina—The retina is not typically the primary site of pathology in acquired posterior segment diseases. Instead, the breakdown of the retinal-RPE-choroidal unit appears to be associated with visual loss[5]. On the other hand, there are genetic diseases, such as retinitis pigmentosa, whereby toxic accumulation of visual cycle proteins results in vision loss. Pharmacokinetic studies have not demonstrated clear advantages of SCS delivery compared with intravitreal or subretinal injections for retinal treatments[28, 32, 88].

4.2.5 Sclera—Few posterior segment diseases affect the sclera. These include scleritis and refractive errors, such as myopia and hyperopia. There have been no published studies targeting these indications via the SCS. Because SCS delivery can achieve high bioavailability within the sclera, if these disease entities are of interest, then approach through the SCS is promising. Subconjunctival delivery can also dose the sclera, although it is hypothesized not to be as effective as SCS injections since IOP induces a natural flow of fluid from the SCS and across/out of the sclera[23, 92]. Scleral permeability was decreased with physiologic and supraphysiologic IOPs compared with IOP of 0 mm Hg[92]. More experiments are needed to explore this further.

4.3 Controlled release

4.3.1 Polymeric controlled release—Because molecules injected into the SCS are cleared quickly, strategies to have controlled release are often desirable. One common strategy is to encapsulate the drug within polymeric microparticles or implants. Monolithic implants have been surgically placed[46, 47] or injected *in situ*[34, 39, 43, 62] within the SCS. They can result in controlled release over months to the SCS and adjacent tissues surrounding the implant.

Particle suspensions injected into the SCS can be spread circumferential around the eye, where the formulation viscosity plays a role in particle spread. In addition, particles ranging from 20 nm to 2,000 nm have been shown to distribute and behave similarly, independent of particle size[81]. Polymeric microparticles can be found in the eye at least 4 months post-injection, suggesting that they are resistant to clearance by the routes molecules clear by[66]. This means that biodegradable polymer microparticles may be most suitable if the objective is for particles to eventually be cleared from the SCS.

Brimonidine-loaded, biodegradable polymeric microparticles injected into the SCS had a therapeutic effect for up to 1 month due to slow drug release from the microparticles[72]. This system achieved a dose reduction to ~13% of the topical dose, probably due to a combination of slow release and localization of the drug near its site of action in the ciliary body[29]. Dose sparing by bolus injection of just 0.02% of the topical brimonidine dose was also seen.

Various biopolymers that can be used to control drug release have been tested within the SCS with good biocompatibility[34, 39, 43, 46, 62, 66]. A significant foreign body reaction to the polylactic acid microparticles was reported, but it was unclear if this was a sterility or biocompatibility issue[72].

4.3.2 Solubility controlled release—Triamcinolone acetonide has been injected into the SCS clinically and in preclinical models, and shown to have therapeutic benefits that can last for months due to slow dissolution of highly water-insoluble drug microparticles[33, 40, 59, 90]. The controlled release behavior may have been aided by drug properties, such as drug binding, that delayed clearance of free molecules[61].

5 Safety and efficacy

Preclinical animal studies suggest that SCS drug delivery has a similar or better safety profile compared with intravitreal injections[33, 34, 59, 68, 82]. Results from completed Phase I/II and II clinical trials (e.g., NCT01789320) have also reported promising safety profiles[73]. While IOP immediately after injection increased with increasing injection volume, IOP returned to baseline within 1 h post-injection[68, 82]. These IOP changes are similar to those observed with intravitreal injections[15, 93–96], and are not expected to cause long-term ocular damage.

Some studies have examined the eye histologically. For example, SCS delivery of hyaluronic acid resulted in retinal atrophy in one study[34], however, no abnormalities were noted. following SCS delivery of bevacizumab and hyaluronic acid in another study[28]. Observation of the eye *in vivo* using indirect ophthalmoscopy after SCS injection of triamcinolone acetonide found evidence of choroidal dilation and hyperemia that resolved by 24 h[68]. The study was unable to identify parameters that affected this finding in a systematic way. No changes in electroretinograms before and after injection were reported, indicating that SCS injection did not adversely affect retinal health[59, 68].

5.1 Human clinical trials

5.1.1 Catheter-based techniques—Incision and catheterization to access the SCS has been performed in human patients. Although a device for this purpose has 510(k) approval, it does not have an indication for use nor have clinical trials demonstrated its efficacy compared with currently available methods. A retrospective analysis was performed on the safety and feasibility of the microcatheter approach to the SCS in a total of 21 subjects[40]. A combination of triamcinolone acetonide and bevacizumab was injected, which improved the best corrected visual acuity and decreased foveal thickness at 1 month[40]. Prospective randomized control trials are needed to more fully determine the safety and efficacy of this approach.

5.1.2 Microneedle injections to access the suprachoroidal space—The safety and efficacy of a microneedle injection containing triamcinolone acetonide is being evaluated in the treatment of macular edema following noninfectious uveitis and retinal vein occlusion. An open-label single-arm phase I/II clinical trial (NCT01789320) demonstrated the safety and efficacy of Triescence (triamcinolone acetonide) in patients who have noninfectious posterior uveitis and significant vitreous haze or macular edema[73]. Nine subjects were enrolled to receive a single unilateral microneedle injection of Triensence and were followed for 26 weeks[73]. All subjects had improvements in visual acuity and reduced retinal thickness, and no change in IOP[73]. There were 38 ocular adverse events reported, the most common being eye pain[73].

A phase II clinical trial (NCT02244032) evaluated the safety and efficacy of a microneedle injection of a proprietary triamcinolone formulation for the treatment of macular edema secondary to noninfectious uveitis. Seventeen subjects received a 4.0 mg dose, and had a reduction in retinal thickness and improvement in best corrected visual acuity. A total of 12

adverse events were reported, the most common of which was eye pain (18%). There was no increase in IOP, which is commonly seen with steroid use intravitreally.

A phase III clinical trial (NCT 03097315) is evaluating the safety and efficacy of a microneedle injection of a proprietary triamcinolone formulation in the treatment noninfectious uveitis. In this ongoing trial, subjects are randomized to receive injections containing either sham or triamcinolone. This trial has the two injections at 12 weeks apart, and the subjects are being monitored up to 24 weeks. Another phase III trial (NCT 02595398) is testing suprachoroidal injection of triamcinolone in the treatment of macular edema associated with noninfectious uveitis. Yet another phase III clinical trial (NCT 02980874) is comparing intravitreal aflibercept with and without simultaneous suprachoroidal triamcinolone injection for the management of macular edema due to retinal vein occlusion.

6 Conclusion

The SCS is a potential space found between the sclera and the choroid, and has become increasingly studied as a route of administration to treat posterior segment diseases of the eye. Due to its close proximity to the sclera, choroid, and RPE, high bioavailability is achievable at these tissues compared with traditional ophthalmic drug delivery techniques. While access to the SCS by sclerotomy and catheterization has been FDA-cleared, it is a surgical intervention that is not in clinical use. Instead, microneedle injection into the SCS is receiving significant attention and is undergoing Phase III clinical trials. Noninfectious uveitis has been the most studied indication both preclinically and in clinical trials. Exploration of additional indications is warranted. Optimizing drug delivery strategies and formulations are the subject of ongoing research. In conclusion, the SCS offers a novel route of administration to the posterior segment of the eye that offers great promise for improved drug targeting to sites of action in sclera, choroid and RPE.

Acknowledgments

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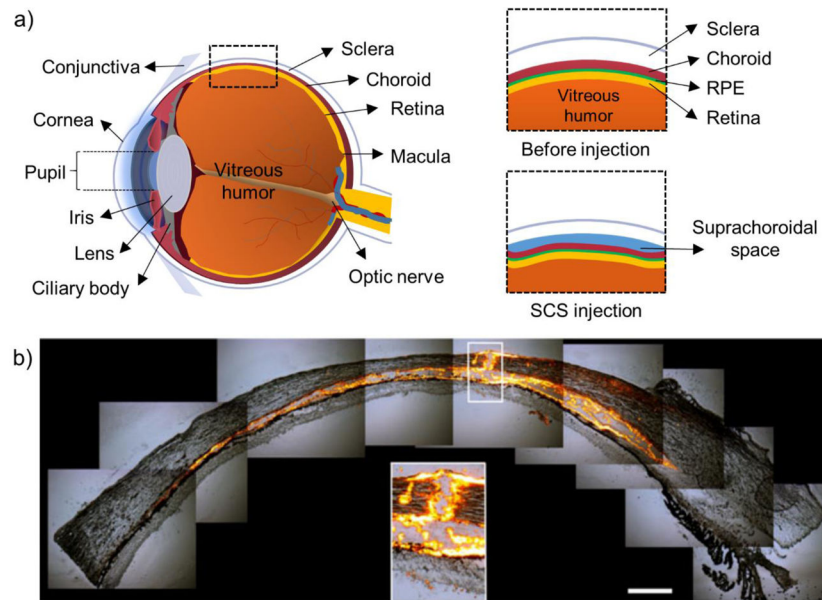
Figure 1.
Diagram of eye before and after suprachoroidal space (SCS) injection. (a) Diagram of eye with relevant anatomy labeled. Insets show before and after SCS injection. (b) Histology of ex vivo porcine eye immediately after microneedle injection of fluorescent particles into SCS.
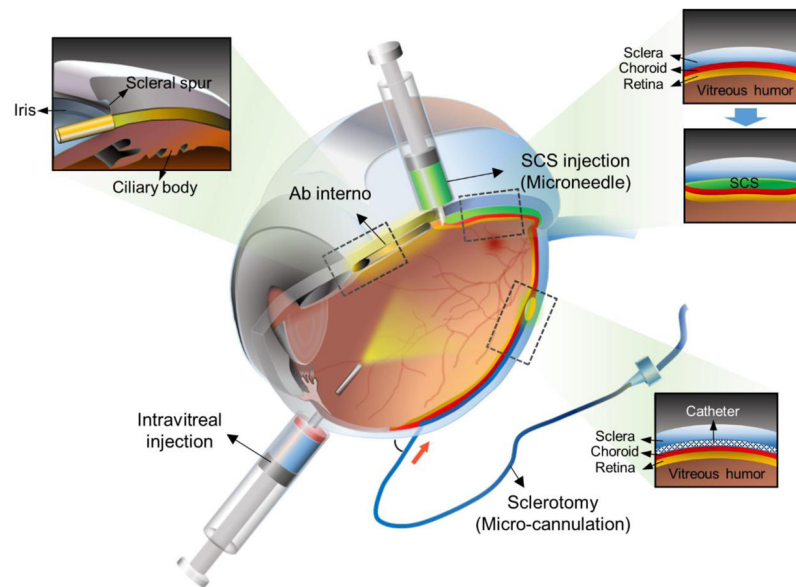
Figure 2.
Diagram of eye highlighting routes of administration to the posterior segment of the eye.
Intravitreal injection enables delivery to the posterior segment and is the current gold
standard. The SCS can be accessed by ab interno surgical technique, by sclerotomy with
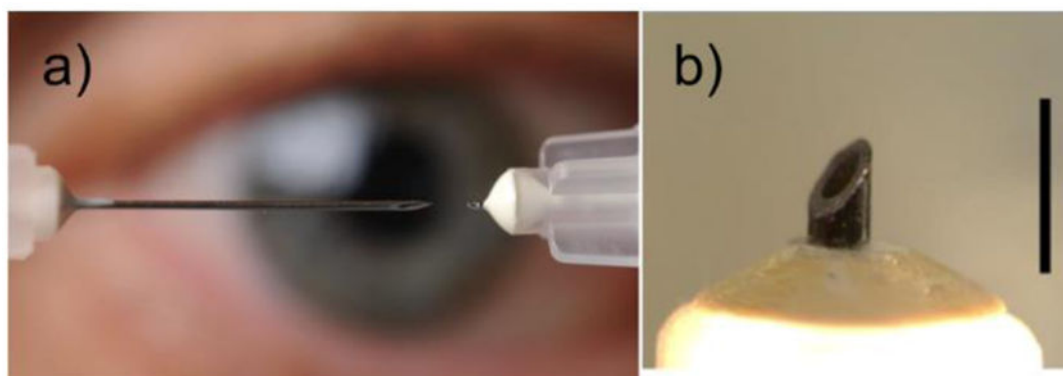subsequent micro-cannulation, or by microneedle injection to the SCS.

Figure 3.
Photographs of microneedle. (a) Photograph of 1½ inch, 30 gauge hypodermic needle (left) and microneedle (right). Reproduced with permission, Gary Meek, Georgia Tech. (b) Magnified photograph of microneedle. Scale bar is 1 mm.
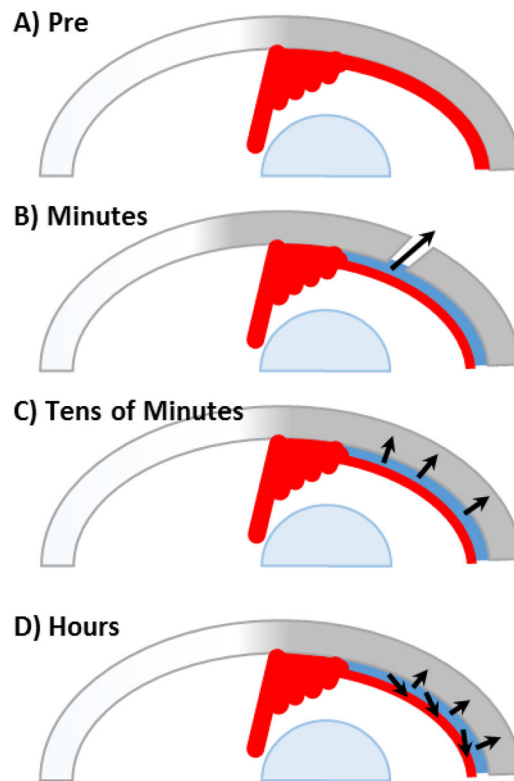
Figure 4.
Diagram of proposed clearance route kinetic regimes. (A) Diagram of eye pre-injection. (B) Pressure-mediated leakage through injection site and perivascular drainage routes. (C) Pressure-mediated trans-scleral movement. (D) Concentration-mediated diffusion and clearance by the choroidal vasculature.

Table 1

Summary of suprachoroidal space access methods

TECHNIQUE	INJECTION SETTING	TARGETING[*]
SCLEROTOMY	Operating room	+
CANNULA	Operating room	+++
AB INTERNO	Operating room	+++
HYPODERMIC NEEDLE	Operating room	+
MICRONEEDLE	Clinic	+(+)[**]

[*] + indicates poor targeting with little to no control over distribution. ++ indicates acceptable drug targeting with some control over distribution. +++ indicates excellent targeting with near total control over drug deposition.

[**] Targeted can be improved through formulation and other methods.