Targeting drug delivery within the suprachoroidal space

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The suprachoroidal space (SCS), a potential anatomical space between the sclera and choroid, is a novel route for drug delivery targeting the chorioretinal layers of the eye. The safety and efficacy of SCS drug delivery have been shown in multiple clinical trials. Recent studies have developed methods for more precise targeting within the SCS at sites of action at the posterior pole (e.g., macula), near the limbus (e.g., ciliary body), and throughout the SCS using iontophoresis, swollen hydrogels, high-density particle emulsions, highly viscous and non-Newtonian fluids, and microstents. Here, we review novel technologies targeting the posterior, anterior, or entire SCS.

Novel drug delivery route: suprachoroidal space

Targeted drug delivery offers the ability to maximize drug effects at sites of action while minimizing off-target effects in other parts of the body. Drug delivery can be targeted to the eye using topical eye drops to target the anterior segment of the eye or intravitreal injections to target the posterior segment [1–3]. However, these delivery methods often provide insufficient targeting. For example, steroids are commonly delivered intravitreally to reduce retinal and/or choroidal inflammation, but these treatments can lead to glaucoma and cataract formation as a result of, at least in part, the drug reaching off-target tissues in the front of the eye because of insufficient targeting [4–6]. Accurate targeting is needed not only to the eye (i.e., as opposed to systemic delivery), but also for sites of drug action within the eye (e.g., choroid, retina, macula, and lens).

Targeting within the eye can be improved by drug delivery to the SCS, which is a potential anatomical space between the choroid and sclera that provides a novel drug delivery route targeting the chorioretinal layer (Fig. 1) [7–9]. Once a drug is injected between the choroid and sclera, the SCS is opened; this allows the drug to flow circumferentially within the SCS from the injection site toward the posterior pole and the macula. Thus, SCS injection can improve the bioavailability of drugs targeting the chorioretinal layer at the posterior segment of the eye and the macula while minimizing delivery into the vitreous humor or the anterior segment. Given its proximity to the highly vascularized choroid, SCS delivery also results in systemic uptake of drug, although at concentrations lower than the local drug concentrations in the eye.

Accessing the SCS has been investigated using several different methods (Fig. 2). Sclerotomy (i.e., cutting across the sclera) can be used to access the SCS using a catheter to inject drug formulations [10]. A related approach is used clinically for *ab interno* placement of glaucoma drainage devices in the SCS [11–13]. However, those approaches are invasive, with associated risks, and must be performed in an operating theater [4].

To address these limitations, hollow microneedles <1 mm in length have been developed to facilitate injection into the SCS. Precisely engineered microneedles can be designed to cross only the sclera, thereby targeting the SCS specifically at the sclera–choroid interface [14–17]. SCS injection using a microneedle is minimally invasive and can be performed as part of a routine clinical office visit. Given that the thickness of the sclera varies among humans and with location in the eye, the length of microneedles can be optimized depending on the location (e.g., 3–5 mm posterior to the limbus) and possibly the patient. Experience has shown that, despite variability, a single microneedle length can be used for a given application (e.g., 700-μm long microneedles can be consistently used to access the SCS in the rabbit) [15,16,18–22]. In several clinical trials, the safety and

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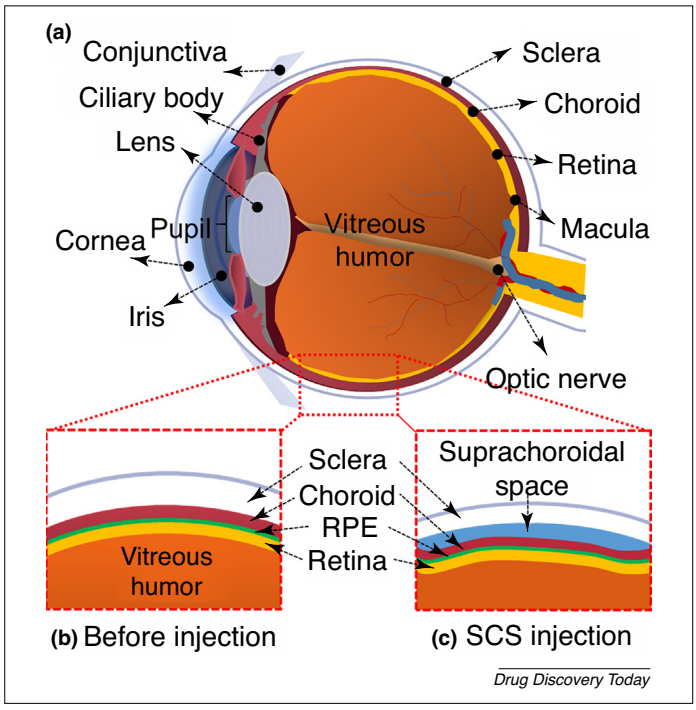

FIGURE 1

Schematic cross-sectional illustrations of the ocular tissues (a) and a portion of the ocular sheath of the eye before (b) and after (c) suprachoroidal space (SCS) injection. Abbreviation: RPE, retinal pigment epithelium.

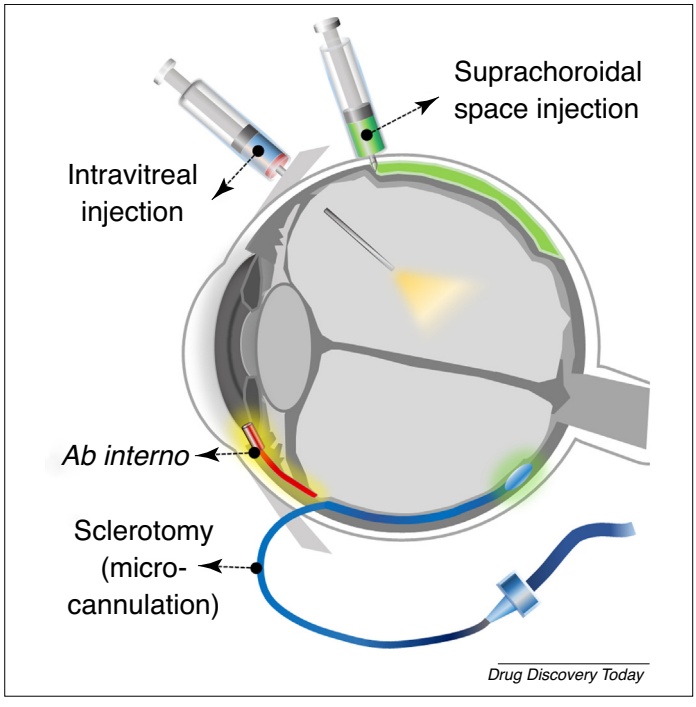

FIGURE 2

Schematic illustration of ocular drug delivery route targeting within the suprachoroidal space (SCS).

tolerability of SCS injection using a microneedle have already been shown [23–26]. Two Phase III clinical trials have been successfully completed in which a triamcinolone acetonide formulation was injected into the SCS in patients with non-infectious uveitis, demonstrating safety of the procedure and efficacy in treatment of macular edema in these patients [24,25]. Most clinical trials of SCS delivery have involved administration of a steroid, which could suppress inflammatory responses to the SCS delivery process. However, most animal studies have not used steroids and have been well tolerated.

Although SCS drug delivery improves targeting of the chorioretina in the eye, there is a need for still better targeting of delivery. Drugs injected into the SCS are spread over large areas of the SCS and do not target, for example, the posterior SCS adjacent to the macula (e.g., of interest for many posterior segment indications, such as macular degeneration) or the anterior SCS adjacent to the ciliary body (e.g., of interest for glaucoma therapy) [20,27]. In other cases, drug should ideally be distributed throughout the SCS for panretinal diseases, such as proliferative diabetic retinopathy [28,29], but conventional SCS injection only distributes drug into a portion of the SCS. To overcome these limitations, targeted drug delivery within the SCS is important to enhance drug efficacy and reduce adverse effects.

Highly targeted drug delivery in the suprachoroidal space

Targeting the posterior suprachoroidal space

For some indications, the site of disease and of drug action is near the posterior pole of the eye, such as the macula. This is the case for indications such as age-related macular degeneration (AMD), diabetic retinopathy, and macular edema, which occur in and around the macula and retina. The macula in particular receives light most precisely in a concentrated region of the photoreceptor cells (rods and cones) at the center part of the retina. Thus, macular diseases result in severe vision impairment. Given that the macula is the most posterior segment of the eye, delivering drugs around the macula with high bioavailability is a crucial issue regardless of efficacy of the drugs [30–32].

Current drug delivery methods generally do not specifically target the macula or posterior pole. Conventional drug delivery routes for the treatment of posterior ocular diseases are topical eye drops and intravitreal injection. Although topical eye drops are easy to administer, only 1–7% of a topically applied drug can pass through the corneal eye layer, and almost none of the drug reaches the macula [33,34]. Intravitreal injection is most widely used for posterior segment therapy, but can cause risk of infection because of its invasiveness. In addition, the vitreous humor where the drugs are infused is not the site of action for treatment of posterior ocular diseases. Advanced ocular drug delivery targeting the posterior segment of the eye, especially around the macula, where most posterior-segment diseases are found, is needed to improve drug bioavailability and efficacy with reduced adverse effects [7,35,36].

Iontophoresis

One approach to target drugs to the posterior pole is through the combination of SCS injection and iontophoresis (Fig. 3a). Iontophoresis is a noninvasive drug delivery method to transfer charged drugs by using a voltage gradient on the tissues [37,38]. Drugs can be transferred by electrophoresis and electroosmosis; delivery by iontophoresis is affected by electric current, length of the electric field, and drug molecular weight and/or particle mass [18,39]. Iontophoresis has been studied for other routes of ocular drug

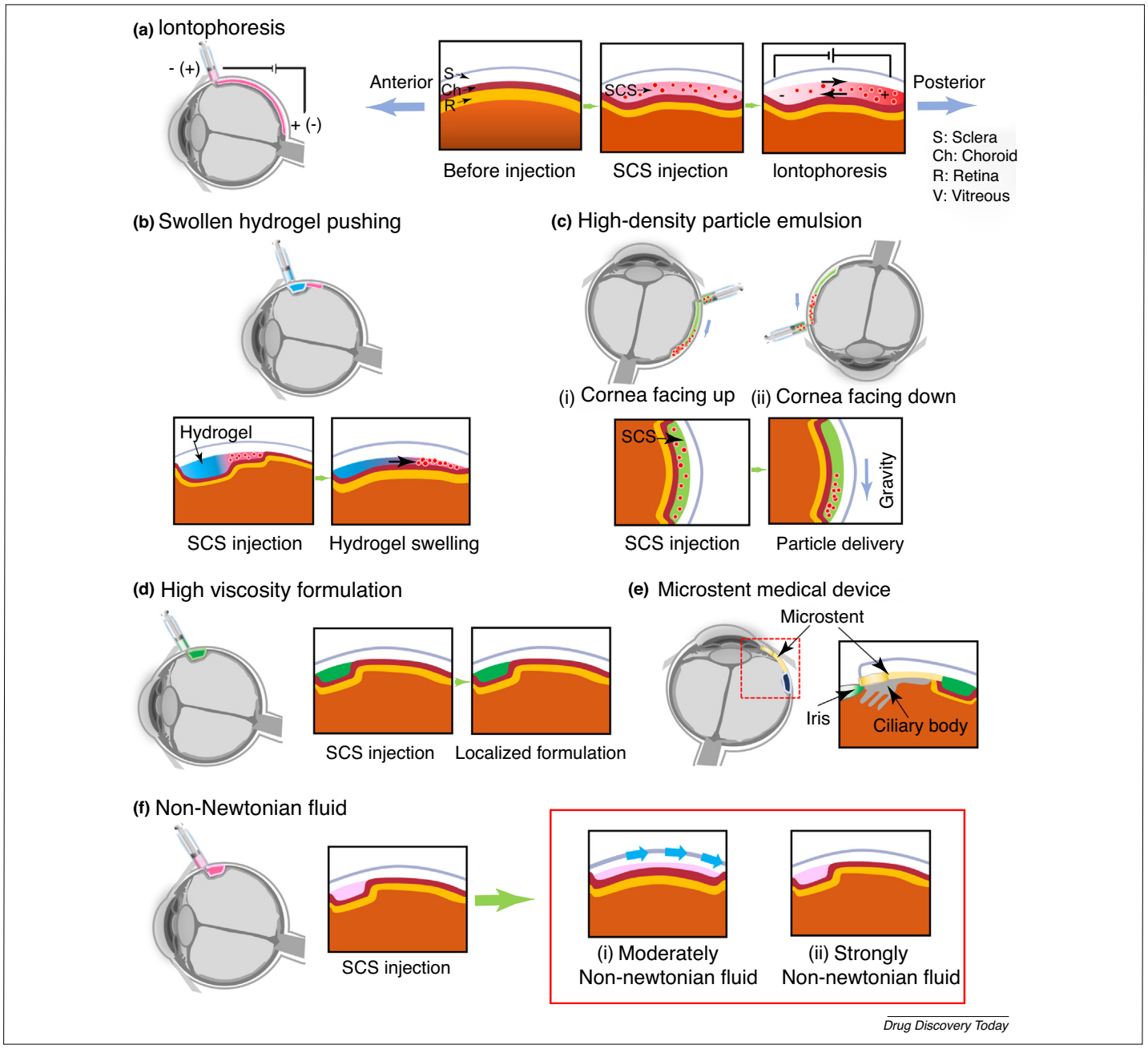

FIGURE 3

Schematic illustration of ocular drug delivery methods that target within the suprachoroidal space (SCS).

delivery, such as transscleral and transcorneal methods. Ocular iontophoresis is not suitable for large molecule and microsphere delivery into the posterior segments because of the dense ocular layers; therefore, Jung and colleagues combined iontophoresis with SCS injection [18]. To apply an electric current, one electrode is embedded in a syringe connected the microneedle, and another electrode is attached to the rabbit ear, such that iontophoresis can be applied in the SCS. By using a microneedle, drug particles can be delivered into the SCS adjacent to the chorioretinal layer by simply passing through the ocular barriers (i.e., the conjunctiva and sclera). As a result, negatively charged nanoparticles and microparticles can be delivered specifically around the posterior pole. In addition, the proportion of particles delivered to the posterior segment was enhanced from 18% to 31% (over 6 mm distance from the limbus). The safety of iontophoresis was confirmed by histological analysis (Table 1).

Given that iontophoresis can control the movement of charged molecules back and forth in the SCS, this technique can be utilized for targeting the anterior part of the SCS. However, there are still many particles around the injection site even after iontophoresis. Additional research is needed for techniques to transfer as many drug particles as possible toward the posterior segment of the eye.

Swollen hydrogel pushing

Another method of moving drug through the SCS toward the posterior pole involves injection of hydrogels that swell in the eye, thereby pushing drug formulations toward the posterior SCS

TABLE 1

Summary of targeted ocular drug delivery methods within the suprachoroidal space (SCS)

Delivery method	Posterior SCS	Anterior SCS	Throughout SCS
Iontophoresis	X	X	
Swollen hydrogel pushing	X		
High-density particle	X	X	
Viscous drug formulation		X	
Microstent		X	
Non-Newtonian fluid			X

(Fig. 3b). Hydrogels have been frequently studied for sustainable drug release due to their biocompatibility and robustness [40–43]. Hydrogels have been modified and conjugated with not only chemicals but also drugs to increase drugs' stability and retention time in the body; injecting hydrogels into the SCS provides a sustainable drug release in the eye. However, injected hydrogel remains near the injection site without spreading backward, making hydrogel injection of drug – including drug-hydrogel conjugates – more appropriate for targeting the anterior segment of the eye than the posterior.

Jung *et al.* reported drug delivery into the posterior segment of the SCS using a hydrogel [19]. In this study, the hydrogel was used as a material to push drugs backward, rather than including drugs in the gel itself. Drug particles were injected into the SCS using a microneedle and pushed from the injection site by a hydrogel due to its high mechanical strength. A hyaluronic acid (HA) hydrogel was used in this study since HA is biodegradable and a component of the vitreous humor [43–45]. Once HA hydrogel is injected, it is swollen and diluted by water influx from surrounding tissues and temperature increase from room to body temperature. Since the swollen hydrogel loses its mechanical strength, it can flow in the SCS. When it flows backward, the particles pushed by the hydrogel at first can be transferred further into the posterior of the eye by the swollen hydrogel. Formulations of a drug particle and an HA hydrogel were loaded in a single syringe. The formulations were prevented from mixing together by controlling their mechanical strengths. In a single injection into the SCS, the drug model nanoparticle was pushed and transferred further backward by the swollen hydrogel. The proportion of particles delivered to the posterior segment of the eye (over 6 mm from the limbus) drastically increased from 13% using injection in 1% HA without hydrogel to 61% with hydrogel pushing, successfully demonstrating drug particle delivery specifically into the posterior segment of the eye by a swollen hydrogel.

Particles located around the initial injection were pushed by a hydrogel and transferred further around the posterior segment of the eye, demonstrating drug delivery targeting only the posterior. In addition, because delivery relies largely on hydrogel pushing, properties of drugs such as size and charge present fewer limitations.

High-density particle emulsion

A third method that has been used to target the posterior pole involves the use of gravity to direct the settling of dense particles in the SCS toward the back of the eye, which are then trapped there once the SCS closes within 1 h after the injection (Fig. 3ci). Particle-stabilized emulsion droplets, which have a high density, were synthesized for posterior ocular drug delivery [21]. The high density of the emulsion was provided by perfluorodecalin liquid, which has a density double that of water. Perfluorodecalin and other perfluorocarbons are widely used in vitreoretinal surgery and clinic imaging applications [46–48]. The nano-sized polymer particles were synthesized for the dual purpose of encapsulating drugs and simultaneously stabilizing the micron-sized emulsions by using the approach of a Pickering emulsion [49,50]. Drug emulsions injected into the SCS can move in the direction of gravity because of their high density, thereby targeting a specific location in the eye. When the eye with cornea facing up was injected with the emulsion, up to 75% of the emulsion was delivered to the posterior segment of the SCS (>6 mm from the limbus) and trapped there once the SCS returned to its collapsed state.

Targeting the anterior suprachoroidal space

Although indications in the front of the eye (e.g., glaucoma) are often treated by topical eye drops, it might be advantageous to inject drug formulations into the anterior part of the SCS to access the anterior segment from behind. Glaucoma is the second leading cause of vision loss worldwide. Primary open-angle glaucoma is the most common form of glaucoma in the USA. Given that glaucoma is asymptomatic, patients might not be aware that they have the disease until severe vision loss has occurred. The pathogenesis of the disease, which increases resistance to aqueous outflow, remains under study. At present, general treatment strategies aim to lower intraocular pressure (IOP) and initial treatment usually starts with administering topical eye drops. Given that the aqueous humor is produced by the ciliary body, many antiglaucoma drugs target the ciliary body to lower IOP [51,52]. In addition, because the ciliary body is located adjacent to the most anterior part of the SCS, drug delivery targeted to the anterior portion of the SCS might be useful for anitglaucoma drugs.

Viscosity of drug formulation

One way to keep drug injected into the SCS near the site of injection (i.e., the anterior SCS near the limbus) is by increasing drug formulation viscosity (Fig. 3d). The site of action of many antiglaucoma drugs is the ciliary body [51,52]. However, the bioavailability of topical eye drops is only ~5% [53,54]. Given that poor targeting causes systemic exposure, 8–53% of patients with glaucoma experience adverse effects [55]. In addition, patient adherence to topical eye drop regimens is as low as 56% [56]. Surgical methods to treat glaucoma, such as trabeculoplasty and trabeculectomy, are invasive and must be performed in the operating room. To overcome the limitations of these conventional delivery methods, Kim *et al.* presented supraciliary space injection of antiglaucoma drugs using a hollow microneedle [22]. The supraciliary space is the most anterior portion of the SCS, located below the sclera and above the choroid and ciliary body. Antiglaucoma drugs targeting the ciliary body, such as sulprostone and brimonidine, were injected into the supraciliary space to maintain high drug concentration at the site of pharmacological action. To improve localization of the drugs around the supraciliary space, 2% carboxymethyl cellulose (CMC) was included in the drug formulation to increase viscosity. Given the high viscosity of the CMC formulation, the drugs stayed around the supraciliary space, decreasing IOP by 3 mmHg. The efficacy of the drugs injected into the supraciliary space was compared with the topical

eye drops containing the same antiglaucoma drugs; an approximately 100-fold dose sparing by supraciliary injection was observed.

Despite the improved targeting, daily SCS injections of antiglaucoma drugs are not likely to find acceptance. To demonstrate sustained release of antiglaucoma drugs and reduce the frequency of SCS injections, Chiang *et al*. encapsulated the drugs into poly (lactic acid) (PLA) microspheres [57]. The microspheres, 20–45 mm in diameter, were prepared by oil-in-water (o/w) emulation solvent-evaporation methods and injected into the supraciliary space using a microneedle. Five percent of the CMC was included in the formulation to increase viscosity so that the microsphere would remain specifically around the supraciliary space. As a result, IOP was lowered by as much as 6 mmHg, and this reduction was maintained up to 35 days.

High-density particle emulsion (targeting the anterior suprachoroidal space)

The high-density particle emulsion (described earlier) enables targeting of the anterior part of the SCS, which is adjacent to the ciliary body (i.e., the tissue that produces aqueous humor for the anterior segment) in the eye when the cornea is facing down (Fig. 3cii). Up to 59% of the emulsion was delivered to the anterior segment of the SCS (<3 mm from the limbus). Thus, versatile emulsion particles could target both the back and front of the eye driven by high density and gravity. However, to provide high density and stability, the ratio of perfluorodecalin should be increased, leading to a decrease the relative drug amount in the formulation. Thus, total injection volumes will need to be increased to deliver the desired amount of drugs using the emulsion.

Microstent medical microdevices targeting the anterior segment of the eye

Microdevices placed in the SCS for glaucoma management can incorporate drugs for local release. The SCS could serve as a site that maintains a local drug delivery device for the anterior chamber. Hovakimyan *et al*. demonstrated this concept with a glaucoma drain (Fig. 3e) [58]. Using two different polymers, they constructed a microstent medical microdevice, attached to a silicone tube that drains aqueous humor from the anterior chamber. The device contained either mitomycin C or paclitaxel, which reduced fibrotic formation to alleviate the incidence of drain clogging in the anterior chamber. The study demonstrated that the implant released paclitaxel for 25 days with an in vitro releasing test. By implanting the devices into the rabbit SCS, Hovakimyan *et al*. found that their drug-eluting suprachoroidal microstent reduced IOP without any significant safety issues. However, the study duration of 6 weeks might not be sufficient to evaluate the potency of the drug.

Distribution throughout the suprachoroidal space

In some cases, drug targets are present throughout the chorioretina, such as in treatment of proliferative diabetic retinopathy [28,29]. Targeting the entire SCS can deliver drugs anywhere, regardless of the site of injection. For example, if uveitis or inflammation is widely spread throughout the chorioretinal layer, targeting all areas of the SCS can effectively deliver the drug to all the SCS regardless of whether the area is wide or narrow. Although increasing injection volume to the SCS makes it possible to deliver drugs to all the SCS area, the volume should be in the safe range. Prior studies in New Zealand white rabbits found that injection of 50–100 μl into the SCS was well tolerated [20,57,59].

Non-Newtonian fluid

A method to target drug throughout the SCS involves the use of non-Newtonian fluid, which is a fluid that does not follow Newton's law of viscosity; its viscosity changes depending on the shear rate. Polymer solutions (e.g., HA, CMC, and methyl cellulose (MC)) that are shear-thinning non-Newtonian fluids can be used for controlled drug release. Kim *et al*. controlled drug particle distribution within the SCS by controlling formulation properties of shear-thinning non-Newtonian fluids (Fig. 3f) [20]. The shear-thinning non-Newtonian fluids have low viscosity at high shear during injection, which facilitated injection into the SCS. By contrast, such fluids have high viscosity at low shear after injection, which keeps the injected formulation localized at the site of injection. However, Kim *et al*. found that a moderately non-Newtonian fluid, such as an HA-based formulation with only moderate viscosity at a low shear rate, facilitated the spread of nanoparticles throughout the SCS over time after injection (Fig. 3fi). This resulted in injected particles spreading over 100% of the SCS. Conversely, a strongly non-Newtonian fluid, such as a CMC- or MC-based formulation with very high viscosity at low shear after the injection, continued to immobilize the nanoparticles mainly at the site of injection, spreading to <20% of the SCS (Fig. 3fii). For comparison, the distribution of nanoparticles injected into the SCS in saline was 29–42% of the SCS. Consequently, drug particle distribution was effectively controlled by utilizing the properties of shear-thinning non-Newtonian fluids.

Concluding remarks

The SCS is a potential anatomical space lying between the sclera and the choroid, and has been studied as a novel route for ocular drug delivery. Safety and tolerability of SCS injections have been demonstrated in Phase III clinical studies. Drug delivery into the SCS targets the adjacent chorioretinal layers with high bioavailability. However, special formulation strategies are needed to enable SCS delivery to target drugs to the posterior (i.e., macula) or anterior (i.e., ciliary body) regions of the SCS, which might be the site of drug action. Targeting within the SCS, the anterior region (i.e., via iontophoresis, high-density particle, viscous drug formulation, or microstents), posterior region (i.e., via iontophoresis, swollen hydrogel pushing, or high-density particles), and whole SCS (i.e., via non-Newtonian fluid), is designed to provide higher bioavailability at sites of drug action with fewer adverse effects. Highly targeted drug delivery within the SCS has been successfully demonstrated by utilizing diverse biocompatible materials as well as properties of the drugs; such drug delivery methods should be optimized further for clinical studies and regulatory approval. In conclusion, targeting drug delivery within the SCS can offer an effective administration strategy with high bioavailability at sites of drug action.

Declaration of interest

M.R.P. is an inventor of patents licensed to companies developing microneedle-based products, is a paid advisor to companies developing microneedle-based products, and is a founder/shareholder

of companies developing microneedle-based products (Clearside Biomedical). This potential conflict of interest has been disclosed and is managed by Georgia Tech and Emory University.

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