

## Suprachoroidal Drug Delivery - A Novel Route for Intraocular Drug Administration

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### ABSTRACT

Suprachoroidal (SC) space offers a unique mode of drug delivery to achieve sustained delivery of therapeutics close to the source of choroidal and retinal pathology like macular edema. It is a novel route of intraocular drug administration with a better safety profile compared to intravitreal route. It bypasses the internal limiting membrane barrier and outer blood retinal barrier and can be a preferred route to target retinal pigment epithelium. It allows larger volume of drugs and longer duration of action with a safer procedure. Recent advances in technology have made it possible to image the SC space, so that it can be utilized for drug delivery and surgical procedures.

**Keywords:** Suprachoroidal space, Macular edema, Intravitreal injection, Drug delivery system, Blood retinal barrier

### INTRODUCTION

Intravitreal drugs administered directly into the vitreous cavity are currently the preferred mode of treatment of a variety of retinal pathologies; however they are limited by the associated posterior and anterior segment complications. The drugs administered into the suprachoroidal space offer a much safer route of drug delivery. Recently it has gained great importance, as a route of drug administration into the eye, to aid in the management of various retinal and choroidal diseases such as age-related macular degeneration (ARMD), polypoidal choroidal vasculopathy (PCV), macular dystrophies, diabetic retinopathy (DR), inflammations of the posterior segment and many such conditions [1].

### Anatomy of the Suprachoroidal Space

The suprachoroidal space is present circumferentially in the eye, lined by the sclera on the outer side and the choroid on the inner [2]. It is a potential space which is normally collapsed and only visible after it has been distended by injection of a drug or dye [3]. Normally on EDI-OCT (Enhanced depth optical coherence tomography) this space is only visible as a hyporeflective band between the choroid and the sclera [4,5]. The thickness of the suprachoroidal space is around 35 $\mu$  [6,7]. It plays an important role in the maintenance of intraocular pressure (IOP) by taking part in the uveoscleral outflow, which is the non-conventional pathway for aqueous outflow and corresponds to about 20% of aqueous outflow [1]. The advent of EDI-OCT has made it much easier to visualize the intricate details of the suprachoroidal space, which was earlier only visible by means of ultrasonography [8,9]. The EDI-OCT uses the standard spectral domain OCT to visualize the choroid.[10] This has been a breakthrough in the suprachoroidal space being used to deliver drugs close to the choroid and retina [2].

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## **Evolution of the Suprachoroidal Space as a Route for Intraocular Drug Delivery**

Drugs can be administered into the eye either topically, systemically, by way of periocular injections, intra-vitreous or suprachoroidal routes [11]. Topically administered drugs in the form of eye drops obtain a bioavailability of only 1-7% in the anterior chamber and that in the posterior chamber is almost negligible [11-13]. Hence this route cannot be used to achieve therapeutic levels of the drug in the posterior segment. Systemically administered drugs are prevented from reaching the retina and the choroid by the presence of the blood-retinal barrier [14]. Periocular injections are widely used by ophthalmologists in the treatment of various choroidal and retinal diseases, but the major drawback is that larger drug molecules are unable to penetrate the sclera and hence one cannot achieve the desired drug levels in the target tissues [14,15]. Periocular injections are also associated with complications such as scleral perforation, scleral melt, elevation in IOP and injuries to extraocular muscles. The intravitreal route is most widely used for drug delivery in the management of various retinal and choroidal conditions throughout the world [16]. Various drugs are currently administered intravitreally like anti-VEGF (vascular endothelial growth factor), steroids, antibiotics and antifungals [16,17]. Although intravitreally administered drugs have a good safety profile, they are not free from complications and require frequent injections to achieve a continued therapeutic dose. The intraocular complications include post injection endophthalmitis, retinal detachment, choroidal hemorrhage, vitreous hemorrhage; as well as anterior segment complications such as elevated IOP and cataract formation [17,18]. The close proximity of the suprachoroidal space with the choroid and the retina ensures that drugs administered into this space will achieve highest concentrations in the target tissues that is the retina and the choroid as compared to any other route of intraocular drug delivery [2,19]. Another very important advantage of this route is that the drug remains compartmentalized and does not diffuse into the anterior segment. Hence anterior segment complications of intravitreal injection such as cataract and raised IOP are hardly seen following suprachoroidal drug delivery [19,20]. The suprachoroidal route also effectively bypasses the sclera and the blood-retinal barrier. The drug delivered into the suprachoroidal space is very close to the target tissue; it thus reduces the amount of drug that is needed to be administered to achieve therapeutic levels [2,19,21-26]. It negates the need for frequent injections and the associated cost of therapy which is very high in case of intravitreal injections [20-26].

The major target tissue for drug delivery via the suprachoroidal route is the choroid. Conditions of the choroid such as central serous chorioidopathy, choroidal melanoma, PCV and non-infectious posterior uveitis are being treated by drugs delivered via the suprachoroidal route. These drugs include corticosteroids, anti-VEGFs and monoclonal antibodies [27-29]. Anti-glaucoma medications can be administered via the suprachoroidal route to achieve glaucoma control [30-32]. Diseases of the retina and retinal pigment epithelium such as ARMD, macular dystrophies, DR can be managed by administration of drugs such as anti-VEGFs and corticosteroids by this novel route [2,19,27,33,34].

### **Access into the Suprachoroidal Space**

There are three techniques to administer drugs into the suprachoroidal space:

1. Standard small gauge needles
2. Surgical cannulation
3. Micro-needles

#### **Standard small gauge needles**

It was the first method to be tried in human models for drug delivery into the suprachoroidal space [35]. It involves direct penetration of the sclera by using standard hollow bore 30 gauge hypodermic needles to enter into the suprachoroidal space [36]. It is a blind procedure and the visualization of

the sclero-choroidal junction is not possible by this method. Hence this procedure has high chances of damaging the choroid or the retina and inadvertent entry into the vitreous cavity [37-39].

### **Surgical cannulation**

It involves a sclerotomy to gain direct access into the suprachoroidal space. EDI-OCT is used to visualize the suprachoroidal space and the sclera-choroidal junction is identified [7-9.] At this point a full thickness scleral incision is made and dissection is continued till the suprachoroidal space is reached. The dissection should be very meticulous and delicate in order to prevent inadvertent damage to the choroid or the retina [27,37]. Once the dissection is complete and the suprachoroidal space is reached, a blunt tipped catheter is inserted through the incision into the space and advanced forward in the direction of the posterior pole. This procedure has to be carried out under direct visualization using a flash diode and a scope. Once the catheter is in the desired position, it is secured with the help of scleral sutures and the drug is injected through the canula into the suprachoroidal space [38,40]. It can also be used to place implants containing depot preparations of drugs into the suprachoroidal space where it will be released in small amounts over a long duration [41].

### **Microneedles**

Being the safest of the three, this method is preferred by most vitreo-retinal surgeons globally. This involves the use of microneedles of 30-33G diameter and having a short length of 0.7-1mm [42]. The length matches the thickness of the normal sclera and hence scleral penetration with such a needle will directly lead into the suprachoroidal space without any damage to the choroid, retina or entry into the vitreous cavity. Following topical or peribulbar anaesthesia, the microneedle is directed perpendicular to the sclera and advanced into the sclera. The length of the needle is such that it stops when it enters the suprachoroidal space. Once the needle has pierced the sclera and hub of the needle is in contact with the surface of the sclera, the drug has to be injected [43,44]. After injection the drug spreads circumferentially and fills up the entire suprachoroidal space [21]. In order to prevent any reflux of the injected drug, the needle has to be kept in this position for about a minute. The suprachoroidal space can accommodate about 1ml of the drug [2,45-47]. However, only 10-50µl of drug is recommended for injection [45,46]. Such a microneedle was first developed by Clearside Biomedical Inc (Alpharetta, GA, USA). They are currently using triamcinolone acetonide 4mg/100µl for suprachoroidal injection for the treatment of non-infectious posterior uveitis (still under trial) [2,47].

### **Pharmacokinetics**

Pharmacological studies have shown that following drug injection into the suprachoroidal space; very high concentrations of the drug are achieved in the choroid and the retina. However, the clearance of the drug is also quite fast and the drug levels usually reach baseline within 40-60 minutes [46,48].

A study was conducted by Olsen W et al. [27] in porcine model to compare the drug levels in the target tissues following injection of Bevacizumab by the intravitreal and suprachoroidal routes. It was found that after 12 hours the concentration of drug in the vitreous was higher in the suprachoroidal group as compared to the intravitreal group. However after 7 days the concentration of drug in the suprachoroidal group was almost negligible; while in intravitreal group it still continued to be high. Another similar study showed that the clearance half-life of drugs administered via the suprachoroidal route was between 3.6 to 7.9 hours [43]. Once the drug is present in the suprachoroidal space it gets eliminated by one of the following ways:

1. Perivascular leakage
2. Trans-scleral movement of drug

3. Diffusion into the choroid [48,49]

### Safety Profile

Suprachoroidal drug delivery is a relatively safe method of intraocular drug administration as it is not associated with the dreaded posterior segment complications as seen with intravitreal injections such as endophthalmitis, retinal detachment, vitreous or choroidal hemorrhage [27,33,40,50,51]. Also the anterior segment complications such as cataract and rise in IOP are not commonly seen with suprachoroidal injections [46,47,50]. However if the volume of injected drug exceeds 30-50 $\mu$ l, a transient elevation in IOP is seen which returns to normal within 60 minutes of injection [40,46].

### CONCLUSION

Suprachoroidal drug delivery is a relatively novel route of intraocular drug administration which is expected to show promising results in the near future. The main advantage of this method is the proximity of the suprachoroidal space with the target tissues which helps achieve very high concentrations in the retina and choroid by administering a very small volume of drug and at the same time avoiding any major posterior or anterior segment complications.

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