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# A Summary of the Advances in Ophthalmic Drug Delivery via Iontophoresis and Microneedles

**Daniel Vettori**[1*]

[1]*Long Island University, USA.*

***Author's contribution***

*The sole author designed, analyzed and interpreted and prepared the manuscript.*

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## ABSTRACT

Drug delivery to the posterior segment of the eye is a significantly challenging task due to the underlying physiological, anatomical and metabolic constraints. Delivery of drugs through ophthalmic route is significantly hindered by multiple physiological processes including potential static and dynamic barriers. Moreover, efflux pumps expressed on ocular tissues severely restrict the intra-ocular penetration of drugs, especially into the posterior ocular tissues. However, severe ocular complications which may be sight threatening, pose an urgency for the intervention/ treatment. Currently, invasive intravitreal injections are widely used to drugs/drug candidates to retina and vitreous body. Therefore, non-invasive drug delivery strategies that overcome the barriers encountered in the ocular milieu should be developed and explored. Various topical formulation approaches are being designed in order to address the safety and patient compliance issues associated with invasive routes. In this review, the targeted drug delivery to the ocular posterior segment via minimally invasive approaches is discussed.

*Keywords: Iontophoresis; ocular; microneedles; invasive; non-invasive.*

**Corresponding author: E-mail: DANVETTORI2016@GMAIL.COM;*

## 1. INTRODUCTION

Delivery of the drugs to the posterior segment of the eye through the topical mode of administration is a difficult task. However, the limitations are needed to overcome for the treatment of posterior ocular disorders. Topical administration of drugs is not yet promising and needs to be addressed with viable alternative optimized formulations owing to concentrations obtained in the eye [1-3]. It is reported that 5-10% of the total dose is available for the ocular tissues following topical instillation. Moreover, systemic administration is not effective due to the higher drug doses required to overcome the blood retinal and aqueous barriers, thus resulting systemic toxicity. Currently, intravitreal injection (i.e., direct injection of a drug into the vitreous body) is reported to be the most unique method of delivering a drug to ocular posterior segments. However, this method of administration is too invasive technique and may lead to complications like retinal detachment, endophthalmitis, cataract, and increased intraocular pressure [4-6]. Drugs when administered via oral route have solubility and permeability issues which in turn has minimum feasibility to reach the site of action and perform at levels where minimum inhibitory concentrations could not be reached.

Minimally invasive techniques like iontophoresis and microneedles are currently the point of interest and are being explored by various research groups to determine the potential possibilities of delivering drugs across various routes like eye, skin etc [7,8]. A summary of the recent advances in ocular delivery using techniques namely iontophoresis and microneedles are summarized below.

## 2. IONTOPHORESIS

Iontophoresis, a minimally invasive technique where a weak electric current is applied to enhance the penetration of ionized molecules into the target tissues [9,10]. The drug of choice is applied along with identically charged electrode and, the oppositely charged alternate electrode is positioned on percutaneous tissue to complete the circuit where the current is conducted [11-13]. The iontophoresis is bound to the principle that in an applied electric field attraction forces are resulted from oppositely charged ions and repulsive forces from identically charged ions. Electrorepulsion aids the drug transfer and drives the ionized drug substances at either the positively charged anode - positive drugs or the negatively charged cathode- negative drugs [12,14]. The transscleral permeability of fluorescein, steroids, antibiotics, antivirals and macromolecules has been enhanced with the aid of iontophoresis reported in literature [15,16]. The concentration of drug, treatment duration, current density, pH, and the drug's tissue permeability are the principal factors that determine the amount of drug delivered by iontophoresis [17]. However, adverse effects such as epithelial edema, reduction in endothelial cell count, inflammatory infiltration and burns are associated with iontophoretic delivery. The extent of burns during the iontophoretic treatment depends upon the site of application, current density and duration of treatment. Reports demonstrated that the detrimental effects could be exerted on the choroid and destroy retinal layers at high current density of iontophoresis [18]. Lam et al. [19] carried out transscleral iontophoresis of dexamethasone sodium phosphate on rabbit eyes using a current of 1.6 mA for a period 25 min. The peak steroid concentrations (Cmax) obtained in the retina-choroidal tissue following iontophoresis, subconjunctival injection (1 mg) or retrobulbar injection (1 mg) were 122, 18.1 and 6.6 mg/g respectively. Results indicated that iontophoresis could deliver markedly higher drug concentrations into the retina-choroidal tissues. Moreover in the vitreous humor, corresponding levels attained were 140, 0.2, and 0.3 mg/mL, respectively. Following iontophoresis, the levels of dexamethasone in the vitreous (3.3 mg/mL) and in the retina-choroid (3.9 mg/g) were maintained for a period of 24 hrs [19]. Hayden et al investigated the plausibility of delivering carboplatin across the rabbit eye using transscleral iontophoresis (20 min at 2.5 mA) and about 45.3 ng/mg of carboplatin levels were found in the retina. An equal amount of the drug levels were found in choroid, optic nerve and vitreous humor. As periocular injections are associated with high risk, transscleral delivery of carboplatin would be a safer alternative accompanied with equivalent therapeutic index and patient adherence [20,21]. Lachaud et al. [22] targeted hydrocortisone acetate (0.1% solution) into rabbit eyes using iontophoresis at a current of 3 mA for 10 min. Results from the study demonstrate that iontophoresis is capable of delivering higher steroid concentrations into rabbit eyes in comparison to topical (0.5%), or subconjunctival (0.1 mL, 2.5%) routes. In human studies carried out by Lachaud et al. [22], iontophoresis at a current strength of 1-2 mA was

adopted for a period of 20 min to deliver dexamethasone acetate (7 mg) for the treatment of a variety of clinical conditions, including idiopathic uveitis. Study corroborated the fact that iontophoresis would aid in achieving therapeutic concentrations of the steroid(s) in ocular tissues. Behar-cohen et al. [23] patented the iontophoresis technique for the delivery of nucleic acid therapeutics into the retinal tissue to promote transient elongation of muller cells in human eye. This elongation of muller cells helps in increasing the permeability of the molecules. The delivery of nucleic acid into retinal tissue holds promising and effective treatment of the retinal diseases, which may be caused by alteration of a gene expression and/or the over-expression of particular growth factors. Diseases like ocular retinopathies including, neovascular diseases and inherited retinopathies such as retinitis pigmentosa can be treated with the retinal delivery. Vollmer et al. [24] studied the delivery and distribution kinetics of aminoglycoside antibiotic Amikacin following transscleral iontophoresis in new zealand white rabbits. Rabbits (*in vivo*) are treated with amikacin solution (concentration 200 mg/mL) at 0,2,3,4 mA DC current for 20 min. Amikacin concentration is highest following the treatment with 4 mA current. The quantitative levels of drug (amikacin) were found in the range of 5.4, 40, 41, 343, and 92 µg/g in the vitreous humor, anterior segment, non-treated hemisphere of the sclera, treated hemisphere of the sclera, and retina/choroid respectively. This study suggests that drug can be delivered using transscleral iontophoresis in reproducible and controllable manner. Binstock et al. [25] delivered methyl prednisolone hemisuccinate (MPH) into the posterior segment of the eye by iontophoresis technique across the rabbit eye using drug loaded hydrogels. Cathodal iontophoresis of 2.6 $mA/cm^2$ was applied for 5 min at the two lateral ends of the scleral membrane. Significantly higher levels of methylprednisolone were found in ocular tissues following 2 hr post iontophoresis. Following 2 hrs of transscleral iontophoretic treatment, the levels of methylprednisolone in retina, aqueous humor, and vitreous were found to be 178.5 ± 21.63 (µg/g), 6.74 ± 2.38 µg/mL, and 2.71 ± 0.57 µg/mL, respectively [26]. Significantly higher levels of drug were obtained in the posterior ocular tissues using iontophoretic treatment. Based on the above studies, it could be inferred that iontophoresis being minimally invasive technique, could serve as viable platform for posterior ocular delivery.

## 3. MICRONEEDLES

In the recent years, minimally invasive microneedles (500 to 750 µm length) have been employed through transscleral route to target therapeutic agents for delivery into the posterior ocular tissues. Drugs either free or encapsulated could be delivered via the sclera in a controlled process. A similar technique was used to deliver sodium fluorescein and pilocarpine. Intrascleral hollow microneedles are also developed for the targeted delivery of the drugs. These microneedles are able to deliver drugs through suprachoroidal, subconjunctival, transcleral routes into the posterior segment of the eye. This delivery system has the capability of delivering nanoparticles, microparticles and drugs in a solution in minimally invasive manner. To deliver microparticles, it is necessary that they are to be accompanied with spreading enzymes such as hyaluronidase and collagenase which help in rapidly hydrolyzing the collagenous and extracellular matrix structure of the sclera so as to make the delivery of microparticles feasible [27]. Jiang et al. [28] attempted to deliver micro and nanoparticles across the human cadaver eye using microneedles where insertion–retraction protocol was used to deliver the soluble molecule and nanoparticles. Hyaluronidase enzyme is required for microparticles to disrupt the scleral structure and obtain similar tissue distribution profile. Infusion of particles into the sclera for modified drug release over time could prolong the drug release into the back-of the-eye. The study demonstrated that an individual needle was capable of delivering 10–35 mL of a fluid, forming a scleral drug depot, which facilitates the subsequent release of the drug into target area. However, further preclinical studies are to be conducted to investigate the efficacy and safety of microneedles to deliver drugs into the posterior segment of the eye. Jason Jiang et al. [28] studied the delivery of solutions containing soluble molecules, poly Lactic acid nanospheres and microparticles using hollow microneedles into the sclera. Infusion volumes of 10-35 uL are delivered into the scleral region. Nanoparticles and soluble molecules were diffused into the sclera but the diffusion of microparticles may be hindered by the collagen fibrils and glycosaminoglucan network and may require the addition of spreading enzymes like hyalouronidase or collagenase to disrupt scleral tissue microstructure. However, the effect of hyaluronidase on the corneal integrity and vitreous body needs to be investigated. Moreover, the factors such as scleral thickness

and infusion pressure did not exert any effect on the transscleral drug delivery. Hollow microneedles deliver drugs through the scleral membrane in minimally invasive manner, when compared to the intravitreal injections administered by the hypodermic needles associated with severe complications like retinal detachment, cataract and infections. Thus microneedles serve as potential and feasible posterior ocular delivery framework in the niche of sustained and controlled release platforms. Samir Kumar et al. studied the suprachoroidal delivery of drug molecules using microneedles to target back-of-the eye. The experiments are carried out using human, cadaver rabbit and pig eyes (*ex vivo*). Microneedles are able to deliver the sulfo-rhodamine nanoparticle and microparticle suspensions to back-of-the eye with infusion volume upto 35 uL and the factors like needle length, retraction pressure and particle size play a crucial role in successful delivery through suprachoroidal space. Suprachoroidal infusion through microneedles would be the minimally invasive strategic drug delivery when compared to periocular and intravitreal injections [29,30]. Geetha Mahadevan et al. [31] formulated the drug delivery device using poly (dimethylsiloxane) substrate with embedded hollow microneedles for the delivery to back-of-the eye. In the study microneedles penetrated the bovine sclera (*ex vivo*) without losing the integrity of the PDMS matrix and was able to deliver 0.02 mg of 6-aminoquinolone into vitreous body and uveal face of sclera without clogging internal needle microchannel. PDMS integrated microneedles facilitate integrated drug targeting and controlled release of drugs by minimally invasive manner compared to conventional needles. Patel SR et al. [32] studied the delivery of fluorescein and fluorescently tagged dextrans, bevacizumab, and polymeric particles (20 nm to 10 µm in diameter) using hollow microneedles in newzealand white albino rabbits. The intensity was monitored and measured using ocular fluorophotometer to investigate the distribution of infused material in the eye compared with fluorescein intravitreal injection. Integrated drug targeting to the suprachoroidal space delivered drug concentration 10-folds higher in the posterior segment of the eye when compared to ocular anterior chamber. But the intravitreal injection primarily targets the vitreous humor apart from posterior and anterior tissues. In contrast polymeric particles (20 nm to 10 µm) remained in the suprachoroidal space and choroid for about a month without the drug clearance and adverse effects. Tyagi et al. [33] studied the drug delivery and distribution in the suprachoroidal space and compared with subconjunctival and intravitreal routes using noninvasive fluorophotometry. In the present study sodium fluorescein (NaF) was infused into suprachoroidal space of Sprague Dawley rats using 34G needle and NaF levels are monitored and compared with posterior subconjunctival or intravitreal injections. However, results indicated that promising drug levels were in the order of suprachoroidal>intravitreal>posterior subconjunctival routes. NaF concentration ($C_{max}$) in choroid-retinal was 36-fold and 25-fold higher after suprachoroidal (2744±1111 ng/mL) injection when compared to posterior subconjunctival (76±6 ng/mL) and intravitreal (108±39 ng/mL) injections, respectively. These results suggest that delivery through suprachoroidal route achieves promising drug levels in the posterior segment of the eye particularly in choroid-retinal tissues. Abbot F Clark et al. [34] patented the delivery of 4,9 (11)-Pregnadien-17α,21-diol-3,20-dione and 4,9 (11) -Pregnadien-17α,21-diol-3,20-dione-21-acetate using cannula through sub-tenon route. The delivery of pharmaceutical active agents through sub-tenon route using cannulae render promising results in the treatment of posterior segment diseases. The cannula developed was successful in localized delivery of the drugs on the sclera and however had the significant potential in the safety aspects when compared to other cannulae used for injection into posterior segments. This cannula has straight proximal end and the distal portion with radius of curvature substantially equal to radius of curvature of globe of human eye. Cannula is inserted below the Tenon's capsule and above the sclera of the human eye at point posterior to a limbus of the eye [33]. Drug is injected through the cannula to form a drug depot on an outer surface of the sclera and then diffuse into targeted posterior tissues of the eye. Gilger et al. [35] attempted to deliver triamcinolone acetonide (TA) into suprachoroidal space (SCS) using microneedles for the treatment of posterior uveitis. Delivery of TA through microneedles to the SCS did not exhibit any signs of adverse effects or toxicity demonstrating safety and effectiveness. SCS injection of low (0.2 mg) and high doses (2 mg) of TA was equally effective in alleviating acute inflammation in the ocular posterior segment when compared to high-dose intravitreal (IVT) injection. The inflammation was not reduced using low-dose IVT TA whereas low-dose SCS TA alleviated the inflammation. The study results indicated that 0.2 mg of SCS TA could arrest the inflammation associated

processes as 2.0 mg IVT TA injection in acute posterior segment inflammation model [36]. Saffar et al studied the pharmacokinetics and biodistribution of bevacizumab following SCS injection using hollow microneedle in the rabbit eyes. This minimally invasive approach forms a depot of bevacizumab between the sclera and choroid, which facilitates and targets drug delivery to respective posterior ocular tissues. Bevacizumab (Avastin®, 1250 µg/50 µL) was injected into the SCS of pigmented rabbits using a metal microneedle measuring 700-800 µm in length inserted 5 mm posterior to the limbus and the tissues were separated and analyzed for the drug concentrations respectively. The percent bevacizumab recovered from the eyes at 15 min, 1 day and 2 days was 88.4±0.9%, 4.6±0.5% and 0.2±0.1% respectively. The distribution of bevacizumab in ocular tissues at 15 min after injection was 76%, 13%, 2.9, 1.0, 0.5, 0.9, 0.6 and 0.1 in choroid, sclera, retina, vitreous, aqueous humor, anterior chamber, lens and optic nerve, correspondingly. After 24 hrs, the levels of bevacizumab in choroid was 34%, 27% in sclera, 23% in retina, 11% in vitreous, 0.7% in aqueous humor, 1.6% in anterior chamber, 3.8% in lens and 0.3% in optic nerve. After 48 hrs, the distribution of bevacizumab was 0.5% in choroid and retina, 3.0% in sclera and aqueous humor, 55% in vitreous, 36% in anterior chamber, 1.1% in lens and 0.6% in optic nerve. Results from the study suggest that formulation should be optimized to sustain the release of drug in posterior segment of the eye [37]. From the view point of the above discussed studies, microneedles appear to be promising platform, when compared to intravitreal injection in terms of sustained/controlled drug delivery.

## 4. CONCLUSION

It's evident that drug delivery to the posterior segment of eye presents significant and considerable confrontations. Established technological platforms namely iontophoresis and microneedles needs to be standardized for optimal penetration characteristics of drug molecules. Advancements in fields of non-invasive drug delivery techniques could explore new avenues for drug delivery to the ocular posterior segments in the near future.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Author has declared that no competing interests exist.

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