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Review Article

Ocular Iontophoresis for Anterior and Posterior Segment Drug Delivery

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Abstract: Over the recent decades, there has been seismic shift in the field of ocular drug delivery ranging from dosage form design to drug product commercialization. Advancements in the fields of nanotechnology, biomedical engineering and clinical science significantly improved the feasibility of ocular drug delivery. Despite these technological advances, there exists need to deliver drugs in therapeutic levels for the treatment of ophthalmic ailments. Strategies improving pre-corneal residence and enhancing transcorneal penetration of drugs/drug molecules showed a promise for targeted delivery. Delivery of drugs through ophthalmic route is compromised by multitude of factors including but not limited to static, dynamic and metabolic barriers. Iontophoresis appears to be a minimally invasive technique to drive molecules into posterior ocular milieu. In this review, recent developments in the iontophoresis technique for delivery of drugs across the ocular globe is summarized and discussed.

Keywords: ocular drug delivery, transcorneal penetration, ophthalmic ailments.

INTRODUCTION

Topical ocular drug delivery systems are developed to treat eye locally to avoid disadvantages of oral and systemic ocular targeting. Topical eye drops are feasible for patient in terms of application but suffers from the inherent draw back that it has poor retentive capacity in the eye and is rapidly drained away from the precorneal cavity by constant tear flow, and further nasolacrimal drainage. Due to these precorneal factors, ocular bioavailability of drugs ranges between 1-5% from topically instilled dose. The dosing frequency of topical eye drops is typically 4 to 5 times a day to maintain a continuous sustained level of medication in the ocular tissues. Ocular drug delivery to the posterior segment of the eye is most challenging platforms ever faced by the pharmaceutical scientists. The design and development of novel topical delivery systems using polymeric gels, colloidal systems, and cyclodextrins has been shown as promising ophthalmic platforms [1]. However, drug delivery to posterior segment of the eye remains as significant challenge through topical route. Ahmed and Patton reported that topical timolol and inulin can penetrate the sclera to enter intraocular tissues after topical application in rabbits, if the corneal route of absorption is blocked [2, 3]. Oral or systemic administration of therapeutic molecules is not effective because of dynamic bloodaqueous and retinal barriers [4, 5]. Intravenous administration is effective to maintain the drug concentrations in the posterior tissues relatively at high doses but pose adverse effects and systemic toxicity. Currently, intravitreal injection is too invasive technique and may lead to retinal detachment, cataract, endophthalmitis and increased intraocular pressure [6-8]. Different routes of administration comprising topical, systemic, intraocular, and periocular (including subconjunctival, sub-Tenon's, and retrobulbar) are widely used to deliver the drugs to posterior tissues of the eye [9-11]. Subconjunctival injection, administration of drug into the region between the conjunctiva and the sclera (subconjunctival space), is proposed to deliver drugs to the posterior segments of the eye through the trans-scleral route. Consequently, periocular and intravitreal routes of administration serve as the promising and ideal platform for the delivery of drugs to the posterior tissues [12, 13]. Depending upon the ophthalmic disease complexity ocular drug-delivery systems may vary from simple topical ocular formulations to systems that require complex engineering solutions, such as intraocular implants, intravitreal injections [14, 15]. Over the last few decades, Iontophoresis technique emerged as minimally invasive platform with respect to wide scope in terms of potential drug delivery and distribution characteristics [16, 17]. This review presents significant developments in the field of iontophoretic ocular drug delivery.

IONTOPHORESIS TECHNIQUE

Ocular iontophoresis is a minimally invasive technique/delivery method where a small and weak

electric current is applied to drive the penetration of ionized molecules into ocular tissues [18]. Over the years, this technique attracted attention among researchers for ionized drug delivery. The optimum pH for iontophoresis is where the drug/drug molecule exists in ionized form. The current is applied at the electrode bearing the same charge as of the drug molecule, and the ground electrode, which is of the opposite charge, is placed elsewhere on ocular tissue to complete the circuit. The drug serves as a conductor of the current through the tissue [19, 20]. The Iontophoresis is bound to the principle that oppositely charged ions attract and same charged ions repel in an applied electric field. The ionized substances are driven into the tissue by electro repulsion at either the anode (for positive drug) or the cathode (for negatively charged drug) [21, 22]. Iontophoresis can be carried out via transorneal/transscleral route depending upon the need with respect to anterior/posterior segment ocular drug delivery. Iontophoresis has been shown to increase the transscleral permeability of many drugs, including fluorescein, steroids, antibiotics, antivirals and macromolecules [23-25]. However, iontophoresis technique is associated with minimal discomfort for the patient. Iontophoresis provides high intraocular drug tissue concentration safely, while minimizing the systemic drug exposure which makes this treatment modality very useful for chronic and long-term intraocular diseases under frequent application. Iontophoresis may have some side effects, which can be due to its application itself or to the administered drug, or the combination of both factors. Reported side effects include localized electrical burns, corneal epithelial or conjunctival edema, mucous discharge, decreased corneal endothelial cell counts which may be due to applying high current densities to small ocular surface. Histopathological changes such as hemorrhagic necrosis, edema, and infiltration of polymorphonuclear cells could be observed [26, 27].

Hughes and Maurice reported that the key factors determining the amount of drug delivered by iontophoresis are current density, duration of treatment, drug concentration, pH, and the permeability of the tissue for the drug molecule [28, 29]. Adverse effects of Iontophoresis include epithelial edema, a decrease in endothelial cells, inflammatory infiltration and burns, the extent of burns depends on the site of application, current density and duration. At higher current densities, iontophoresis has been shown to damage the choroid and destroy retinal layers [30]. Hayden B and colleagues studied the pharmacokinetics and toxicity of systemic versus focal subconjunctival and transscleral Coulomb controlled iontophoresis (CCI) of carboplatin administration in the rabbit eye [31, 32]. Lam *et al* carried out trans scleral iontophoresis of dexamethasone sodium phosphate on rabbit eyes using 1.6 mA current for 25 minutes. The peak steroid concentrations(c_{max}) detected in the retinal-choroid tissue following iontophoresis, subconjunctival injection (1 mg) or retrobulbar injection (1 mg) are as follows 122(mg/g tissue) for iontophoresis, 18.1 for subconjunctival injection, and 6.6 for retrobulbar injection. Results indicated that iontophoresis delivered high drug concentrations in the retina choroidal tissue. Moreover, in the vitreous humor, corresponding values were 140, 0.2, and 0.3 mg/mL, respectively. Even 24 hours after iontophoresis, significant therapeutic levels of dexamethasone remained in the vitreous (3.3 mg/mL) and in the choroid-retina (3.9 mg/g) [33]. Hayden *et al* attempted to deliver carboplatin employing transscleral Iontophoresis (20 min at 2.5 mA) to the rabbit eye. Peak carboplatin levels in the retina were found to be (45.3 ng/mg). Similar results were found for the choroid, vitreous humor, and optic nerve. Provided the risks associated with periocular injections, trans scleral delivery of carboplatin would seem to be a safer, equally effective choice for therapeutic application [34, 35]. Lachaud *et al* performed iontophoresis for delivery of hydrocortisone acetate (0.1% solution) into rabbit eyes using a current of 3 milliamperes (mA) for 10 minutes. The present study demonstrated that iontophoresis could deliver higher concentrations of steroid into rabbit eyes than topical (0.5%), or subconjunctival (0.1mL, 2.5%) routes. In human studies, Lachaud used iontophoresis to deliver dexamethasone acetate (7 mg, 1–2mA, 20 min) and treat a variety of clinical conditions, including idiopathic uveitis. Study concluded that iontophoresis would achieve therapeutic concentrations of the steroid(s) in ocular tissues [36]. Behar-cohen *et al* developed and patented the iontophoresis technique for the delivery of nucleic acids therapeutics in to the retinal tissue to promote transient elongation of muller cells of 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 significant 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 human ocular retinopathies including, neovascular diseases (Age-Related Macular degeneration, Diabetic Macular Edema, etc.) and inherited retinopathies such as retinitis pigmentosa can be treated with the retinal delivery. A flexible ocular iontophoretic device fabricated by batch processing, is reported by Zhang et al. Manganese ions as a tracer for detection of optic nerve damage were delivered into rabbit eyes by this iontophoretic device. Under 1 mA for 600 s, the average Mn^{2+} concentration in the eye ball after iontophoresis was 102 ng/ml, while the one in the control group was 23 ng/ml. Using 2 mA for 600 s, the average concentration was 271 ng/ml, while it was 38 ng/ml in the control group. Thermal injury during iontophoresis was not observed under an applied current of no more

than 2 mA for no longer than 10 min, with the local temperature less than 38 °C, measured by an infrared thermal imager [37]. Vollmer, et al studied the delivery and distribution kinetics of aminoglycoside antibiotic Amikacin following transscleral iontophoresis in newzealand white rabbits. Rabbits (in vivo) are treated with amikacin solution (concentration 200mg/ml) at 0,2,3,4 mA DC current for 20mins. Amikacin concentration is highest following the treatment with 4mA current. Drug concentrations in the tissues at this current were approximately 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 [38]. Binstock *et al* [39] delivered methyl prednisolone hemisuccinate (MPH) into the posterior segment of the eye by iontophoresis technique. (MPH) iontophoresis was studied in rabbits, using drug-loaded hydrogels. Cathodal iontophoresis of 2.6 mA/cm^2 was applied for 5 min at two opposite sites on the sclera. Ocular drug levels [40] were determined 2 h after iontophoretic treatment Significantly higher methylprednisolone levels were found in ocular tissues after iontophoresis. Two (2) h after the trans-scleral iontophoretic treatment, 178.5 ± 21.63 (µg/g), 6.74 ± 2.38 µg/ml, and 2.71 ± 0.57 µg/mL were found in the retina, aqueous and vitreous humor respectively. Sekijima et al investigated the feasibility of ocular iontophoresis across isolated rabbit cornea and conjunctiva in terms of transport enhancement, tissue viability and integrity using various model permeants namely Lidocaine hydrochloride (a cationic compound), sodium benzoate (anionic compound), and fluorescein isothiocyanate labeled dextran (molecular weight 4400 Da, FD-4, hydrophilic large compound). The fluxes across the cornea and conjunctiva for drugs were significantly increased by the application of electric current by several folds. The trans epithelial electric resistance recovered on the tissues following application of electric current suggesting that tissues maintained integrity and viability [41]. An ocular iontophoretic device using a biocompatible planar PEDOT electrode is developed by Yushi *et al.* The device can be placed under the eyelid and deliver ions through a small area on the eyeball, reducing tissue damage during ion penetration. The concentrations observed in the *in vivo* experiments was 396 ng/mL, while the efficiency observed in the controlled experiments was only 2.69 ng/mL. The temperature distribution was simulated and measured, and thermal injuries were not observed under an applied current of 1.5 mA [42].

CONCLUSION

Challenges pose to be significant in the ocular drug delivery, the data presented hold promise for delivery of drugs in breaching the ocular barriers. Novel technologies need to be primarily designed and to be developed to provide sustained action, enhance bioavailability, improved patient safety and minimal adverse effects. Eventually, multidisciplinary integration of delivery technologies to optimize drug bioavailability is needed. Ocular iontophoresis is a promising local delivery system for charged drugs/drug molecules. Exploration of interactions in the eye tissue during electric current application and better design of devices and probes could open avenues in iontophoretic application for the intervention of long term ocular complications.

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