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

Abstract

Drug delivery to the posterior segment pose significant challenges to pharmaceutical scientists owing to physiological and anatomical constraints put forth by the eye. Delivery of drugs through ophthalmic route is significantly hindered by multiple physiological processes including potential static, dynamic barriers. Moreover, efflux pumps expressed on ocular tissues also confronts delivery of drugs, especially to the posterior segment. However severe ocular complications pose urgency for the treatment. Therefore, drug delivery strategies that overcome the barriers posed by these routes should be developed and explored. Currently, invasive routes like intravitreal route is widely used to deliver therapeutic entities to retinal tissue and various topical formulations are being developed to overcome the challenges posed by this route of administration. In this review, we discuss the approach of targeting drugs via non-invasive approaches across the ophthalmic routes.

Keywords: Iontophoresis, Ocular, Microneedles, Invasive, Non-Invasive

INTRODUCTION

Drug delivery to the posterior segments of the eye is highly challenging task. However, the limitations are needed to overcome the treatment of the sight threatening posterior ocular diseases. 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). Moreover, systemic administration is not effective prior to high drug doses, toxicity, blood retinal and aqueous barriers. Currently, intravitreal injection (i.e., direct injection of a drug into the vitreous body) is reported to be the most promising and unique method of delivering a drug to ocular posterior segments. However, this method of administration is too invasive technique and may lead to retinal detachment, cataract, endophthalmitis and increased intraocular pressure (2, 3). Drugs when administered via oral route have solubility and permeability which in turn has minimum feasibility to reach the site of action and perform at levels where minimum inhibitory concentrations could not be reached(4, 5).
Non-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 (6, 7). A summary of the recent advances in ocular delivery using non-invasive techniques like iontophoresis and microneedles are summarized in the current review.

**IONTOPHORESIS:**

Iontophoresis is a non-invasive technique in which a weak electric current is applied to drive and enhance the penetration of ionized molecules into tissues (8). In this technique, the drug is applied with electrode bearing the same charge as of the drug molecule, and the ground electrode, which is of the opposite charge, is placed elsewhere on percutaneous tissue of the body to complete the circuit. The drug serves as a conductor of the current through the tissue (9). 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 electrorepulsion at either the anode (for positive drug) or the cathode (for negatively charged drug) (10). Iontophoresis has been shown to increase the transscleral permeability of many drugs, including fluorescein, steroids, antibiotics, antivirals and macromolecules (11, 12). 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 (13). 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 (14). 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 (Cmax) 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-choroid. 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) (15). Hayden et al attempted to deliver carboplatin employing transscleral Ionotphoresis (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 (16, 17). 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 (18). Behar-cohen et al patented the iontophoresis technique for the delivery of nucleic acids 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 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 and inherited retinopathies such as retinitis pigmentosa can be treated with the retinal delivery (19). Vollmer et al studied the delivery and distribution kinetics of aminoglycoside antibiotic Amikacin following trans-scleral iontophoresis in new zealand 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 trans-scleral iontophoresis in reproducible and controllable manner(20). Binstock et al 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/cm² was applied for 5 min at two opposite sites on the sclera. Ocular drug levels were determined 2 h post iontophoretic treatment. Significantly higher methylprednisolone levels were found in ocular tissues after iontophoresis. Post 2 hours 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 humor, and vitreous, respectively (21, 22).
Microneedles

Recently, coated microneedles with a length of 500 to 750 µm have been utilized in trans-scleral drug delivery for the targeted delivery of therapeutic entities to ocular tissue, as they can be used in a minimally invasive manner. The needles can be used to deliver free as well as encapsulated drugs via the sclera in a controlled manner. Sodium fluorescein and pilocarpine were coated and delivered using a similar technique. Intrasceral 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 eye. This delivery system is able to deliver microparticles, nanoparticles, and drugs in a solution in minimally invasive manner. To deliver microparticles, accompanied administration of spreading enzymes such as hyaluronidase and collagenase is also prominently required. These enzymes rapidly hydrolyze the collagenous and extracellular matrix structure of the sclera making the delivery of microparticles feasible. Jiang et al attempted to use microneedles to deliver model drug in the form of micro and nanoparticles using human cadaver eyes. The soluble molecule and nanoparticles were delivered using an insertion–retraction protocol, whereas the microparticles needed hyaluronidase to disrupt the scleral structure to obtain similar tissue distribution. Infusion of particles into the sclera for controlled drug release over time could facilitate extended therapies in the back of the eye. The study demonstrated that an individual needle was able to deliver 10–35 mL of a fluid into the sclera, forming an intrasceral drug depot for 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 in posterior eye delivery. Jason jiang, et al 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 glycosaminoglycan network and may require the addition of spreading enzymes like hyalouronidase or collagenase to disrupt scleral tissue microstructure. However the effects of hyaluronidase on the corneal integrity and vitreous body is to be studied and investigated. Moreover, the factors like Infusion pressure and scleral thickness did not effect the delivery of drug molecules through the sclera. Hollow microneedles delivers drugs through the scleral tissue in minimally invasive manner, compared to the intravitreal injections administered by the hypodermic needles which includes severe complications like retinal detachment, cataract
and infections. Thus microneedles serve as alternative posterior drug delivery agents in the
niche of sustained and controlled release platforms (23). Samir kumar et al studied the
delivery of drug molecules using microneedles to back of the eye through suprachoroidal
space. The experiments are carried out using human, cadaver rabbit and pig eyes (ex vivo).
Microneedles are able to deliver the sulforhodamine nanoparticle and microparticle
suspensions to back of the eye with infusion volume upto 35uL and the factors like needle
length, retraction pressure and particle size play crucial role in successful delivery through
suprachoroidal space. Suprachoroidal infusion through microneedles would be the minimally
invasive strategic drug delivery when compared to pericocular and intravitreal injections (24,
25). Geetha mahadevan, et al 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 breaking or
delaminating the PDMS matrix and 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 offer integrated drug targeting and controlled release of drugs by
minimally invasive manner compared to conventional needles (26). Patel SR et,al studied the
delivery of fluorescein and fluorescently tagged dextrins, bevacizumab, and polymeric
particles (20 nm to 10 µm in diameter) using hollow microneedles in newzealand white
albino rabbits. The fluorescence 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 posterior segment of the eye when compared
to anterior chambers. But the intravitreal injection primarily targets the vitreous humor apart
from posterior and anterior tissues. In contrast polymeric particles (20nm to 10 µm) remained
in the suprachoroidal space and choroid for a period of months without the drug clearance
and adverse effects (27). Tyagi, et al 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 (28). Abbot F.Clark et al 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 subtenon route. The delivery of pharmaceutical active agents through subtenon 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. 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 (29). Gilger et al attempted to deliver triamcinolone acetonide (TA) into suprachoroidal space (SCS) using microneedles for the treatment of posterior uveitis. Delivery of TA to the SCS with microneedles was promising and effective, with no signs of adverse effects or toxicity. SCS injection of low (0.2mg) and high doses (2 mg) of TA was as effective in reducing acute inflammation in the ocular posterior segment as high-dose intravitreal (IVT) injection. Low-dose SCS TA was also effective in reducing inflammation; however, low-dose IVT TA was not. Results from this study suggest that 0.2 mg and 2.0 mg of SCS TA was as effective in reducing inflammation as 2.0 mg IVT TA injection in a model of acute posterior segment inflammation (30, 31). Saffar et al studied the pharmacokinetics and biodistribution of bevacizumab following SCS injection using hollow microneedle in the rabbit eyes. This minimally invasive approach deposits bevacizumab between the sclera and choroid, which targets drug delivery to respective posterior 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 analysed for the drug concentrations respectively. The percent bevacizumab recovered from the eyes was 88.4±0.9% at 15 min, 4.6±0.5% at 1 day, and 0.2±0.1% at 2 days after injection. The distribution of bevacizumab in ocular tissues at 15 min after injection was 76% in choroid, 13% in sclera and 2.9% in retina, 1.0% in vitreous, 0.5% in aqueous humor, 0.9% in anterior chamber, 0.6% in lens and 0.1% in optic nerve. After 1 day, drug levels were 34% in choroid, 27% in sclera and 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 2
days, the distribution of bavacizumab was 0.5% in choroid, 3.3% in sclera, 0.5% in retina, 55% in vitreous, 3% in aqueous humor, 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 to posterior segment of the eye (32).

CONCLUSION:-

It’s evident that drug delivery to the posterior segments of eye presents significant and considerable confrontations. 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.

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