Occular Iontophoresis- A Review On Basic Principles

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Abstract

Ocular drug delivery remains as one of the most challenging field of drug delivery. The major drawback encountered during the use of conventional ocular drug delivery is the poor bioavailability issue of the applied dosage form. Over the recent years there has been significant shift in the methodology or approaches to ophthalmic drug delivery system which includes alteration in the dosage form design which in turn increases the capacity to carry maximum concentration of drug at targeted site of eye. Ocular iontophoresis is a non-invasive technique that utilises low voltage electric current for the delivery of the drug. Iontophoresis technique has now gained worldwide attention. They are used to enhance the bioavailability of drug, better absorption and faster delivery of the drug. This review summarizes the basic principle of ocular iontophoresis and iontophoretic devices and its application in ophthalmology.

Keywords- *Ocular, corneal absorption, iontophoresis, ocular bioavailability*

INTRODUCTION

The eye is one of the vital and sensitive organs of our body. It helps us to connect us to the external world. Diseases related to eye are a common problem nowadays. Various drug delivery systems and devices suitable for the treatment of eye related problems have been developed. Major portion of the eye is not accessible to the systemic delivery of drug, hence topical route remains as the most preferred one. However conventional ocular drug delivery system suffers from certain drawbacks which include –

1. Barriers to ocular drug delivery system
2. After an eye drop instillation typically less than 5% of applied dose reaches intraocular tissue.
3. Pre-corneal loss leading to low bioavailability.
4. Actual corneal permeability of drug is quite low.
5. Normal resident value of 7µl of eye drains out the maximum volume of dose instilled onto the eye [1].

Hence an ideal ophthalmic drug delivery was developed to sustain the drug release and remain in the vicinity of the front of the eye for prolong period of time. Optimization of ophthalmic drug delivery, was attained by addition of polymers of various grades, development of viscous gels, development of colloidal suspension or using erodible/non-erodible insert to prolong the pre-corneal drug retention [2,3]. Cornea offers more resistant to negatively than positively charged compounds [4].

Following characteristics are required to optimize ocular drug delivery system [5]:

- Good corneal penetration
- Prolonged contact time with the corneal tissue thereby reducing pre-corneal drug loss.
- Simplicity of instillation for the patient.
- Non irritant and comfortable form.
- Suitable pH of the dosage form
- Appropriate rheological properties and concentration of the viscous system. On application of the dosage form blurred vision must not occur.
- Must be relatively non-greasy.
- Reduction in frequency of administration to aid patience compliance.

Physiochemical Property of Drug for Ocular Drug Delivery

Transcellular or Paracellular pathway is the main route for drugs to penetrate across corneal epithelium. Hydrophilic drugs penetrate primarily through the paracellular pathway, which involves passive or altered diffusion through intercellular space while lipophilic drugs prefer transcellular route. Lipohilicity, solubility, molecular size and shape and degree of ionisation affect the route and rate of drug penetration in cornea [6].

Drug properties and the eye

If a drug is not already in solution, it must dissolve very rapidly to be absorbed through the cornea due to rapid and extensive losses of the drug after application to the front of the eye [7]

- Drugs with poor water solubility may be presented as oily solutions, ointments, emulsions or suspensions.
- Drugs absorbed through the cornea are modestly lipophilic with a partition coefficient of between 10 and 100.
- Small, hydrophilic drugs (molecular weight ≤500) may enter via paracelllular tight junctions.
- Drugs that are not stable in solution may be prepared as powders for reconstitution or solid inserts.
- Drugs applied to the eye are subject to relatively low enzymatic activity.
- Drugs may be administered as prodrugs and be activated by esterases (Dipivefrin and Latanoprost).
- The drug targets in the anterior segment are found on the surface of the eye and beneath the cornea and are accessible to drugs applied to the front of the eye. Drug receptors in the posterior segment are inaccessible from the front of the eye and must be injected.

Ocular bioavailability [8]

Ocular bioavailability is essential determinant in the effectiveness of any particular dosage form. Physiological factors that can affect a drug's ocular bioavailability include protein binding, drug metabolism, and lachrymal drainage. Protein bound drugs do not penetrate the corneal epithelium owing to the size of the protein molecule and the drug complex [9]. Because of the brief time an ophthalmic solution may remain in the eye, the protein binding of a drug substance can quickly negate its therapeutic value by render in GIT unavailable for absorption. Normally, tears contain 0.6% to 2.0% of protein, including albumin and globulins, but disease states can raise these protein levels. Although ocular protein binding is reversible, tear turnover results in the loss of both bound and unbound drug [9].As in the case with other biologic fluids, tears contain enzymes (e.g., lysozyme) capable of metabolic degradation of drug substances. However, in the last few years various researches have been conducted on the ocular metabolism of pharmacologic agents with a background on latest technology [11, 12**].**

Barriers to ocular drug delivery

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Even though the lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to the naso-lacrimal duct rapidly in a couple of minutes.

1. **Lacrimal fluid-eye barriers:-**Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal barrier is formed upon maturation of the epithelial cells. They migrate from the limbal region towards the centre of the cornea and to the apical surface. The most apical corneal epithelial cells form tight junctions that limit the paracellular drug permeation. [13] Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs [14].
2. **Drug metabolism—**many enzymes (cytochrome P450, aldehyde oxidase, aldo/ketone reductase, cyclooxygenase, monoamine oxidase, hydrolase, and transferase) are present in ocular tissues such as cornea, lens, iris-ciliary body and retina. These enzymes have the capacity

to metabolize the active drug thereby leading to decrease in ocular drug bioavailability [15].

3. **Drug binding to tear proteins—**Tear fluid contains approximately 0.7% of total body protein. Drug binding to these tear proteins may result in a reduction in concentration of total available free drug for required pharmacological action at the target site [16].

4. **Melanin binding—**The melanin pigment present in the iris and ciliary body may also change the ocular bioavailability of a topically administered drug [15] Drugs such as ephedrine and timolol have a high binding capacity for melanin, and only a very small portion of the bound drug can release at a very slow rate.
5. **Blood-ocular barriers:-**The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells. This barrier prevents the access of plasma albumin into the aqueous humor, and limits also the access of hydrophilic drugs from plasma into the aqueous humor. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but thereafter distribution into the retina is limited by the RPE and retinal endothelia [15].
6. **Physiological barriers** include (i) tear turn over, (ii) naso-lachrymal drainage and (iii) blinking. Anatomical barriers comprise of static and dynamic barriers, which limits drug entry into the anterior segment. Static barrier consists of corneal epithelium, stroma, and blood–aqueous barrier (BAB). While dynamic barriers involved in conjunctival blood and lymph flow as well as tear drainage [15].

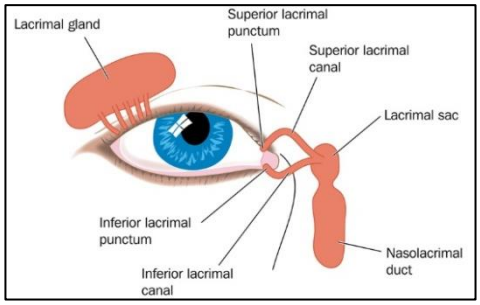

Fig.1: Naso- lacrimal drainage system

Various Ocular Drug Delivery Systems

1. **Nanotechnology in ocular drug delivery system-** Nanoparticles are solid, submicron, colloidal particles ranging in dimension from 10 to 1000 nm, in that drug molecules may be present in dissolved, entrapped, adsorbed or covalently attached form. Based on formulation approaches nanoparticles can be acquired with distinct properties and release attributes for the capsulated drug.
2. **Ocular inserts-** Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems [17].
3. **Lacrisert-** Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and was introduced in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea. It dissolves in 24 hours.Lacrisert has not been applied as a drug delivery carrier as yet [18].
4. **SODI-** Soluble ocular drug insert (SODI) is a small oval wafer. It is inserted into the inferior cul-de-sac and gets wets and softens in 10-15 seconds. After 10-15 min the film turn into a viscous polymer mass, after 30-60 mins it turns into polymer solutions and delivers the drug for about 24 hours [19].
5. **Iontophoresis-** It has non-invasive nature of delivery to both anterior and posterior segment. It requires a mild electric current

which is applied to enhance ionized drug penetration into tissue. This mode of delivery can overcome the potential side effects associated with intraocular injections and implants mentioned earlier.

6. **Microneedle-** This hollow tubed microneedle can serve as a route for targeted drug delivery for retinal disease using an array of delivery suspensions such as microbeads and microbubbles [20].
7. **Liposomes-** The use of liposomes as atopically administered ocular drug delivery system began in the early stage of research into ophthalmic drug delivery. Drug's physicochemical properties have significant influence on the effect of liposomes. Favourable result with liposomes found essentially with lipophilic drugs as hydrophilic drug escape rapidly out of the liposomes than lipophilic drugs.
8. **Implants-** Intraocular implants are specifically designed to provide localized controlled drug release over an extended period. These devices help in circumventing multiple intraocular injections and associated complications. Usually for drug delivery to posterior ocular tissues, implants are placed intravitreally by making incision through minor surgery..

Iontophoresis in Ocular Drug Delivery

Iontophoresis is a non-invasive technique, whereby electric current is used to deliver the charged or neutral molecule via any synthetic or biological membrane. It helps to increase the penetration of ionized drug. The process needs a small amount of weak electric current for the delivery of drug (charged molecule). The technique for ocular Iontophoresis was first developed by German Scientist Wirtz in 1908, who conducted experiment by passing the electric current through the electrolyte saturated cotton sponges for the treatment of various eyes diseases [21].

Due to high charge density and high solubility the salt form of the drug is used. Ionized drug concentration in the solution should range from 0.01-5% [22].

Principle

The iontophoretic technique is based on the general principle that like charges repel each other. Thus during iontophoresis, if delivery of a positively charged drug (DC) is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode. On application of an electromotive force the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body. Communication between the electrodes along the surface of the skin has been shown to be negligible i.e. movement of the drug ions between the electrodes occurs through the skin and not on the surface. When the cathode is placed in the donor compartment of a Franz diffusion cell to enhance the flux of an anion, it is termed cathodal iontophoresis and for anodal iontophoresis, the situation would be reversed. Neutral molecules have been observed to move by convective flow as a result of electro-osmotic and osmotic forces on application of electric current [23].

Ocular Iontophoresis utilises low voltages (<10 V), and low currents (~ few mili-amperes) over long periods (minutes to tens of minutes or more) to provide a sustained and regulated driving force [24].

The increased flux during iontophoresis would include [25].

1. Flux due to the electrochemical potential lgradient across the skin.

2. Change in the ocular permeability due to the applied electric field.

3. Electro-osmotic water flow and the resultant solvent drag.

$J_{ionto} = J_{electric} + J_{passive} + J_{convective}$

$J_{electric}$is the flux due to electric current application; $J_{passive}$ is the flux due to passive delivery through the skin; and $J_{convective}$ is the flux due to convective transport due to electro osmosis.

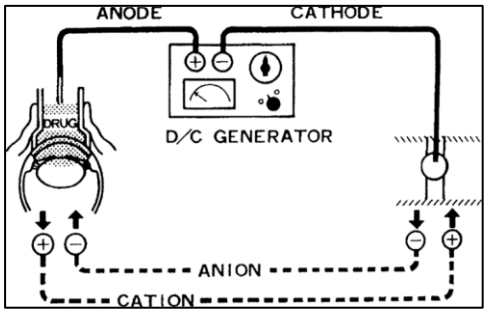

Fig. 2: Ocular iontophoresis of positively charge drug

Types of Iontophoresis

Trans-scleral iontophoresis

For topically applied drugs, lens-iris diaphragm is the main barrier to posterior tissues of the eye such as vitreous and retina. Transscleral iontophoresis passes this barrier and delivers drugs to the vitreous and retina through the choroid. The iontophoretic device is placed on the conjunctiva, over the pars-plana area to avoid current damage to the retina. Transscleral iontophoresis proves to be an effective alternative for multiple intravenous injections or systemic therapy used for posterior ocular disorders, such as retinitis, optic nerve atrophy, uveitis, endophthalmitis, pediatric retino-blastoma and age related macular degeneration (AMD).

Trans-scorneal iontophoresis

Transcorneal iontophoresis delivers a high concentration of drug to the anterior segment of the eye (cornea, aqueous humor, ciliary body, iris, and lens) used for the treatment of anterior segment diseases, such as: glaucoma, dry eyes, keratitis, corneal ulcers, and ocular inflammations [33]. Transcorneal iontophoresis does not have the potential to penetrate a drug into posterior segment of the eye [34].

Iontophoretic Devices:-The Devices used for Drug Delivery are:-

I) Ocuphor- Ocuphor is composed of polyacetal sponge and is used for transscleral iontophoresis. The drug applicator is a silicon shell that contains a silver-silver chloride ink conductive element, a hydrogel pad for drug absorption and wire that is acting as dose controller.

II)Visulex- Visulex is made from unique membrane, which increases drug transportation and eliminate the non drug ions hence acting as the prime carrier for the transfer of drug-ions through the sclera tissue [35].

III)Eyegate- Eyegate is in annular shape and made up of soft silicon rubber. The annular well is made up of tungsten electrode which is immersed in the solution of drug which flows through the silicon tubes. The solution is infused in one chamber and in other air bubble is aspirated that maintain negative pressure this help to maintain the contact of the device with the eye [36].

Basically, iontophoretic devices consist of continuous DC source and two electrodes. The ionized drug is placed in the vicinity of electrode compartment that has the same charge, while the ground electrode location is elsewhere on the body surface.

Table 1: References of drugs with ionophoretic conditions and tissue studied.

Drug	Iontophoresis Condition	Tissue
Acetylsalicylic acid [26]	5 mA/cm^2 , 10 min	*In vivo* rabbit eye
Acyclovir [27]	0.5 mA/cm^2, 5 min	Porcine eye
Dexamethasone [28]	5.1 mA/cm^2 ,4 min	*In vivo* rabbit cornea
Gentamycin sulphate[29]	0.8 and 2 mA/cm^2 , 1 min	*In vivo* rabbit cornea
Ketoconazole [30]	4-6 mA/cm^2 , 15 min	Rabbit eye
Vancomycin [31]	2.55–10.2 mA/cm2, 120 min	Rabbit sclera
Riboflavin-5-phosphate [32]	1 mA, 5 min	*In vivo* human cornea

Approaches for Iontophoresis

There are numerous approaches for the drug delivery by iontophoresis devices. These include:

The most commonly used method is filling the eye cup with drug solution and submerging a metal electrode which is extended from the current supply into the solution. The 5-10 mm eye cup is placed over the eye. During the iontophoresis the drug is infused to the cup continuously. There are two ports on the eye cup: one for delivery of the drug solution and the other for holding the metal electrode and aspirating air bubbles. The ground electrode is placed usually in the animal's ear close to the first electrode, which have minimum resistance [37]. Eye cup has different shapes including an annular shape silicone probe, which is used for transscleral iontophoresis (called Eyegate, Optis, France). Its opening is 13 mm which avoids contact with cornea [38, 39].

The second approach is delivery probe containing drug saturated gel. Jones and Maurice [39] firstly use this method to delivered fluorescein into the anterior chamber of the eye, by using a fluorescein-saturated agar-gel.

The gel was filled into a plastic tube and was partly extruded from the tube to make a direct contact with the eye. Later Grossman [41] and Frucht- Pery [42, 43] used the same concept with gentamicin-saturated agar for trans-corneal and trans-scleral iontophoresis in rabbits. However, the use of agar was unacceptable since the agar material was fragile and left remains of agar on the eye surface, which were not approved to the eye.

Iontophoretic Models [44]

For the drug delivery there are various models that are being proposed on these techniques. Some of the models are ophthalmic based and some are transdermal based.

Ophthalmic Based: Ophthalmic based models like *in vitro* and *in vivo* are summarized below.

I) *In Vitro* Model: One of the examples of the in vitro model that was used for the ocular drug-penetration evaluation was the agarose gel. It was used as the model for transdermal Iontophoresis, later the diffusion properties of some local anaesthetics from the solution of drug to the 1% agarose gel that was cast in syringes with tops cut off. The motility of drug at different pH values. The motility of drug was measured by the help of paper electrophoresis by determining spot migration.

II) *In Vivo* Model: In ocular Iontophoresis there are two approaches for the delivery of the drug. It can be either through Transcorneal or Transscleral Iontophoresis.

A) Trans-corneal Iontophoresis: It delivers drug at a high concentration in the anterior part of eye that is cornea, aqueous humor, ciliary body, iris and lens and this helps to treat the diseases that happen in the anterior segment of eye like keratitis, glaucoma, dry eyes, corneal ulcers and ocular inflammations.

B) Trans-sceleral Iontophoresis: The diaphragm of lens and iris limits the entry of the drug to the posterior tissue of eye that is vitreous humor and retina. It crosses the barrier of posterior segment. The device is placed over the parsplana area to avoid the damage to conjunctiva by the current. It is an alternative for systemic therapy and used to cure the posterior ocular disorder [45]

Factors Affecting the Iontophoretic Delivery of Drugs

Physiochemical properties-

1. Molecular size and molecular weight: smaller and more hydrophilic ions are transported at a faster rate than larger ones. The permeability coefficients in positively charged negatively charged and uncharged solutes across biological membrane are a function of molecular size.
2. Charge: for amino acids and peptides the transport of cations are better than the anions. However an increase in charge will require a decrease in pH . This in turn will decrease the electroosmosis and the electrotransport process.
3. Polarity: Hydrophilic compounds are ideal candidates for optimum flux.
4. Concentration: an increase in concentration was shown to increase the apparent steady state flux of a number of drugs.

Drug formulation-

1. Effect of pH: pH of the bio-membrane plays an important role in transfer of ions in presence of electric field. For iontophoretic delivery of drugs the pH should be optimum in which the compound exists in ionized form.
2. Ionic strength: ionic strength is directly proportional to permeation of drug. Some authors reported that increasing the ionic strength of the system decreases the permeation of drug and has no significant effect upto 0.5 V.
3. Presence of co-ions: an ion of equal charge but different type is referred as co-ion. The buffering agent used to maintain the pH of donor medium is the source of co-ions. Co-ions generate more mobile and smaller ions than the drug ions. Hence a competition occurs between the co-ions and the drug which results in reduction in fraction current carried by the drug.

Experimental factors-

1. Current strength: there is a linear relation between the observed flux of a $1cm^2$ where the current is limited to 1mA due to patient comfort considerations. This current should not be applied for more than 3 minutes because of local irritation and burns. For safe use 0.5 mA/cm^2 is applied.
2. Current density: it is quantity of current deliverd per unit surface area. The current density should be sufficient enough to provide desired drug delivery rate.
3. Pulsed current: the continued use of DC can reduce the iontophoretic flux because of polarisation effect. This can be overcomed by using pulsed current.
4. Duration of application: the iontophoretic penetration of drug linearly increased with increasing application time. However for safety considerations current is not applied more than the specified time for a particular drug.

Biological factors-

1. Intra and inter subject variability is reduced in iontophoretic technique.
2. Regional blood flow affects iontophoresis upto a very small extent.

Advantages of Iontophoresis:

Advantages of Iontophoresis technique are as follows:

1. The technique is painless when properly applied.
2. This technique is an alternative to injection and helps to deliver ionized and unionized drugs. It improves the delivery of polar molecules and high molecular weight compounds.
3. The risk of infection is reduced since the treatment through this technique is non-invasive in nature.
4. It is less time consuming. Treatment is completed within a minutes.
5. It reduces potential for tissue trauma reducing the variability between the individuals, as the drug delivery rate is dependent on applied current.

Disadvantages of Iontophoresis:

The disadvantages of Iontophoresis technique are as follows:

1. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.
2. An excessive current density usually results in pain.
3. Burns are caused by electrolyte changes within the tissues.
4. The safe current density varies with the size of electrodes.
5. The high current density and time of application would generate extreme pH, resulting in a chemical burn.
6. This change in pH may cause the sweat duct plugging perhaps precipitate protein in the ducts, themselves or cosmetically hyperhydrate the tissue surrounding the ducts.
7. Electric shocks may cause by high current density at the skin surface .

8. Possibility of cardiac arrest due to excessive current passing through heart.
9. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.
10. High molecular weight 8000-12000 results in a very uncertain rate of delivery[46]..

Applications [44]

Iontophoresis has gained its applications in different fields that is helpful for the delivery of variety of drugs. The various applications of Iontophoresis are as follows:

A) Topical delivery -The ability to control the delivery rates of drugs by changes in current makes iontophoresis an attractive technique to use in topical delivery of wide range of drugs.

B) Ophthalmology-Iontophoresis has been used experimentally to deliver antibiotics into the eye." The principal disadvantage of this technique is the time required for direct contact of the electrode with the eye.

C) Hyperhidrosis-It is a common disorders; this technique is used to cure plantar and palmar hyperhidrosis. For the treatment to cure this disorder the current is passed at the strength just below the threshold and the infected region is kept in the tap water for approximately 30 minutes. It is safe and effective process.

D) Diagnosis of Cystic Fibrosis-The device used to cure the cystic fibrosis is iontophoresis of pilocarpine. This technique is commonly used in paediatrics.

E) Anaesthesia-The use of anaesthesia is used in superficial wound excisions, eyelid surgery, local skin biopsies. The major disadvantage of anaesthesia is pain, distortion of tissue, potential systemic absorption. The disadvantage of anaesthesia was overcome by the use of Iontophoresis technology.

F) In Physical Therapy-In physical therapy corticosteroids are the prime drug. They are so used because they have profound anti-inflammatory effect, less effective and can be administered in both oral and topical. Various corticosteroids are available in the form of water soluble salts, possessing negative charge and hence move towards the respective electrode in the presence of electric current.

I). Dentistry -Dentistry, probably to an even greater extent than physical therapy, has used iontophoresis. The use of iontophoresis for three basic applications in dentistry are:-

(i) Treatment of hypersensitive dentin

(ii) The application of local anaesthetics to produce profound topical anaesthesia, as is done in some physical therapy applications.

G). Non-invasive monitoring of glucose -Electro osmotic flow generated by application of low level current has been used for extraction of glucose through the skin. As the direction of glucose flow is in the opposite direction (in outward direction in skin) to conventional iontophoresis, it is called reverse iontophoresis.

Conclusion:

The present scenario of ocular iontophoresis proves its clinical potential and importance as a local delivery system for many drugs. A better knowledge of tissue interactions within the eye during electric current application, along with better design of devices and probes adapted to the site of application, will result in better intra-ocular penetration of drugs and such points are needed to be studied via experimentation. The iontophoretic treatment is already a promising tool for delivering anti-inflammatory and antibiotic drugs to the eye. Various experiments are needed to determine the ability and the capacity of this technique to deliver a variety of other chemotherapeutic agents, to treat other bacterial infections, to determine safety over an extended period of time, and to determine efficacy in humans.

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