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A REVIEW ON RECENT TRENDS AND FUTURE PERSPECTIVES OF IONTOPHORESIS ASSISTED OCULAR DRUG DELIVERY

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Keywords:

Iontophoresis, Ocular drug delivery, EyeGate®-II drug delivery, OcuPhore® hydrogel, Trans-corneal iontophoresis and Trans-scleral iontophoresis and ophthalmic route

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ABSTRACT: Iontophoresis assisted drug delivery system refers to a novel system for delivery of the drug in a non-invasive and effective manner across the skin or biological membranes by electrical assistance. Drug substances exhibiting low trans-corneal (ocular) permeability can be effectively delivered in a safe, fast, and painless manner by the employment of electric current of low intensity, which enhances permeation of drugs across the cornea and thereby, extends the duration of drug action. Fundamental principles of physics guide the technique of ocular iontophoresis that repulsion occurs between the ionic charges of the same nature, while attraction occurs between the ionic charges of opposite nature. Electro-repulsion and electro-osmotic flow are the two transport mechanisms on which ocular iontophoresis works. For the ocular delivery of the drug, there are various iontophoresis devices available in the market, *e.g.*, Eyegate® II and OcuPhore®, those are the most commonly used delivery devices for this purpose, while Visulex™ is another similar system. On the basis of the site of application, ocular iontophoresis can be classified as trans-scleral and trans-corneal. This review paper is aimed to provide a comprehensive and comparative account of the development of ocular iontophoresis devices comparing their principle, factors affecting iontophoretic drug delivery, their therapeutic applications, and future prospects.

INTRODUCTION: Topical ocular drug delivery with effective and adequate ocular bioavailability remains a challenging task for scientists owing to the eye's distinctive and impervious anatomy and physiology. Various complicated and invasive routes are sometimes explored, like sub-conjunctival injection, periocular injection, intra-vitreal injection, and surgical implants for adequate and localized ocular drug bioavailability.

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Ocular iontophoresis was, therefore, explored as an effective and non-invasive alternative method for effective ocular drug delivery in case of various vitreoretinal (posterior segment) diseases responsible for provoking visual impairment and blindness including diabetic macular edema (DME) and diabetic retinopathy, age-related macular degradation (AMD), uveitis, cytomegalovirus (CMV) retinitis, endophthalmitis, and retinal vein occlusion.

To treat these diseases effectively, the therapeutic concentration of the drug must be targeted to the tissues of the eye while at the same time minimizing systemic effects. The routes available for delivering a drug to the eye are topical, systemic, intravitreal and periocular.

Although, some of these routes (intravitreal and periocular) may deliver the effective drug concentration to a vitreoretinal area of the eye, while the conventional topical route is ineffective to attain therapeutic concentration because of the drug's drainage *via* the nasolacrimal duct, low corneal permeability due to the presence of discrete barriers in the eye. As compared to the other drug delivery routes, the ocular drug delivery or ocular route is a sophisticated route because of the presence of numerous ocular barriers [1-3].

There are three types of barriers in ocular drug delivery:

1. Static Barriers:

- It includes blood-aqueous and blood-retinal barriers and cornea, retina, and sclera.
- These barriers rely on the lipophilicity, charge, molecular size of the drug molecules.

2. Dynamic Barriers:

- It includes tear dilution, conjunctival and choroidal blood flow, efflux pumps, and lymphatic clearance.
- These barriers rely on the various fluids transport proteins and ion transporter.

3. Metabolic Barriers:

- It includes cytochrome P450 and lysosomal enzymes induced metabolic and enzymatic breakdown of drugs.

Among the various prevalent routes of ocular drug delivery, *i.e.*, topical, systemic, intravitreal and periocular, none of them were adequately effective and acceptable due to drawbacks like shorter corneal drug retention, lower drug permeation, non-productive systemic drug absorption, patient discomfort and associated complexities [4]. Various novel drug formulation approaches, *i.e.*, nanovesicles, nanoparticles, in-situ gelling systems, were also developed and explored for effective ocular drug permeation precluding drawbacks of the conventional methods of ocular drug delivery [5]. However, effective drug targeting to the posterior segment of the eye remains unmet, and therefore, ocular iontophoresis is being extensively studied for enhancing the ocular drug bioavailability.

A complex human eye is compartmentalized into two distinct chambers: Anterior and Posterior chamber. Anterior chamber consists of cornea, iris, conjunctiva, ciliary body, aqueous humor, and lens, while the posterior chamber comprises of choroid, sclera, neural retina, vitreous humor and, retinal pigment epithelium (RPE) [6].

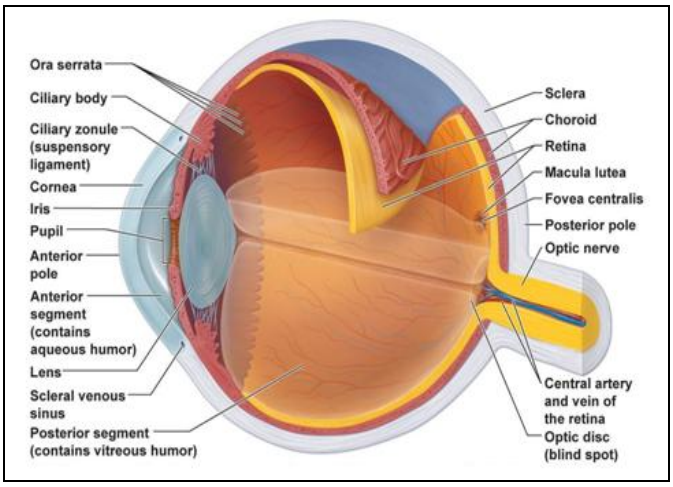


FIG. 1: STRUCTURE OF HUMAN EYE

The eyeball consists of three surrounding layers:

- The outer covering (Transparent Cornea and White Sclera).
- The middle layer/uveal coat (Choroid, Cilliary body, and Iris).
- The interior layer (Retina).

History of Ocular Iontophoresis: The iontophoresis mediated drug delivery system has been used for many years, and some remarkable research work has been done by scientists that are continuously in progress. During the mid 18th century, the application of electric current in delivery of the drug was investigated by William James Morton (1846-1920) and Stephen Leduc (1856-1939) for the first time. Until the 20th century, the electrically assisted drug delivery was known as "cataphoresis," which was later introduced by the new term "Iontophoresis" by Fritz Frankenhauser (1968). The German scientists, Wirtz in 1908, firstly examined ocular Iontophoresis for the treatment of ulcers of the cornea as well as keratitis by applying low-intensity electric current on the eye globe through cotton sponges saturated with the electrolytes [7-8].

Iontophoresis for Ocular Drug Delivery: Ocular iontophoresis or electrically assisted ocular drug delivery is a tool in which a high concentration of an ionized drug is transported into anterior as well as posterior portion of the eye with the help of a low intensity direct electric current. Iontophoresis relies on the fundamental principle of physics that similar charges repel and opposite charges attract one another. This approach has been widely studied for ocular delivery of antiviral, antibacterial, antifungal, anti-metabolites, genes, and steroidal drugs to the eye. Intraocular injections and surgical implants may lead to various side effects which could be overcome by the employment of ocular iontophoresis [8-9].

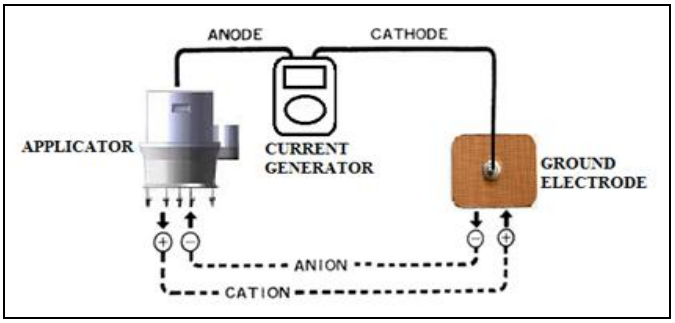


FIG. 2: SCHEMATICS OF OCULAR IONTOPHORETIC DEVICE

Advantages of Ocular Iontophoresis:

- It is applicable for delivering large drug molecules to eye, *e.g.*, corticosteroids.
- It is a painless, easy, and needle-free delivery system.
- It eliminates the chances of drug dilution and elimination through tear fluid.
- It may overcome drawbacks like blurred vision, irritation, poor ocular bioavailability, patient discomfort, the limit of low drug dosing, as in the case of the conventional delivery system.
- It also avoids the occurrence of bleeding, infection, local injuries, and retinal detachment commonly observed in intraocular injections and surgical implants [10-11].

Disadvantages of Ocular Iontophoresis:

- Multiple applications of transscleral ion-tophoresis may cause complications such as hemorrhagic necrosis of chorioretinal tissues, disruption of retinal construction, RPE hyperplasia, and fibrosis at the site of iontophoresis.

Factors Affecting Ocular Iontophoresis: There are various factors that affect iontophoresis based ocular drug delivery, *e.g.*, physicochemical properties of a drug compound, equipment/device for drug delivery, and drug formulation based factors.

TABLE 1: FACTORS AFFECTING OCULAR IONTOPHORESIS

Physicochemical factors	Device related factors	Drug formulation factors
Molecular size	Current density	pH
Charge	Current strength	Partition coefficient
Concentration	Duration of action	
Polarity	Type of electrode	

Physicochemical Factors of Drugs: Various physicochemical characteristics of drug compounds like molecular size, charge, concentration, and polarity may alter the ion transfer significantly [12].

Molecular Size: Molecular size of drugs affects iontophoretic delivery and quantity of drug transported. Highly hydrophilic and smaller ions show rapid transport than the larger ions, but this could still be an alternative delivery for macromolecules showing poor absorption.

Charge: Charge of the drug molecule is another important transporting factor that also determines the mechanism by which iontophoresis will work, *i.e.*, Electrorepulsion or Electroosmosis. Hence, increment in charge will require decrement in pH, which leads to a decline in the electroosmotic and electrorepulsion process.

Concentration: High drug concentration is delivered to the targeted ocular site in a fast and safe manner by iontophoresis. The solubility of the drug is high in its salt form because of dissociation, and hence, the salt form of the drug is chosen for iontophoresis [6, 13].

Device Related Factors: The equipment or device used for ocular iontophoresis are of various types with a different type of electrodes and application, but the basic working unit and mechanism of iontophoretic drug administration in all equipments is same.

Current Density: It is defined as the amount of current delivered per unit area of the surface (mA/cm^2). For ocular iontophoresis, the contact surface area may alter with different equipment employed, *e.g.*, OcuPhor hydrogel has a 0.5 cm^2 contact surface area. The current applied for trans-corneal, and trans-scleral drug delivery is usually up to 1.8mA/cm^2 and 5.5 mA/cm^2, respectively [14].

Current Strength: It is the intensity of direct current applied and controlled by the device. The electric current is maintained at optimum condition by a battery-operated portable device up to 1mA at a particular period of time. The current strength for ocular iontophoresis is higher than the transdermal delivery, and it is usually 5mA approximately [8].

Duration of Application: The amount of drug transported is directly proportional to the duration of current applied. For ocular iontophoresis, the application time for drug delivery is approximately 10-20 min.

Type of Electrode: The electrode design assures that tear fluid does not dilute the drug solution and also provides a containment seal that keeps the drug inside the electrode. Various electrodes have been designed as per the needs, including polycarbonate, o-ring seal, silver wire, silver CDE (current distribution element) of IOMED Inc. [15], and biocompatible planer PEDOT electrode [16].

Drug Formulation Related Factors:

pH: The pH of the drug solution should be either below 6 or above 8, since the drug will be ionized at eye's physiological pH, *i.e.*, pH 7.4 of tear fluid [2].

Partition Coefficient: The cornea is made up of lipophilic epithelial and endothelial cell layer between which hydrophilic stromal cell layer is present and, therefore, the drug with both hydrophilic as well as a lipophilic character may easily permeate cornea [17].

Transport Mechanism in Iontophoretic Drug Delivery: Iontophoresis is established on the principle that oppositely charged ions attract whereas similarly charged ions repel one another. The transport mechanisms through which iontophoresis proceed or ion-transport takes place into a deeper section of the eye are electorepulsion and electroosmotic flow and both the mechanisms depend on the flux enhancement for small ions.

Electrorepulsion is the process of developing a mild electric field or ionic-electric field interaction between the cathode electrode (for –ve charge drugs) or the anode electrode (for +ve charged drugs), and this is also known as 'Nernst-planck effect'. Magnetic resonance imaging using Mn^{2+} ions is used to visualize ion accumulation in the vitreous and aqueous segments of the eye following anodal iontophoresis through sclera and cornea.

Electroosmotic flow is a bulk fluid flow across a semi-permeable membrane down the concentration gradient, which acts as a driving force for molecular transport. It can also be defined as an electrically forced flow of charged ions across a semi-permeable membrane, which leads to a coupled flow of solvent. It is achieved by the application of a voltage across charged membranes under physiological conditions when the epithelium is negatively charged [18].

For ocular drug delivery, the passive diffusion is the main area to focus because the permeability barrier of ocular membranes is not as effective as of stratum corneum, so both the mechanisms follow passive diffusion. The total drug flux $F_{(TDF)}$ is expressed as the sum of passive flux $F_{(P)}$, electrorepulsive flux $F_{(ER)}$, and electroosmotic flux $F_{(EO)}$ as shown in equation 1.

$$F_{(TDF)} = F_{(P)} + F_{(ER)} + F_{(EO)} \quad \text{...(Equation 1)}$$

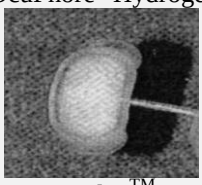
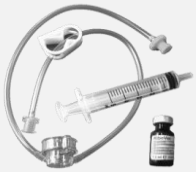
At steady state, substitutions for the terms describing $F_{(P)}$, $F_{(ER)}$ and $F_{(EO)}$ gives:

$$\begin{aligned} F_{TDF} &= F_{(P)} + F_{(ER)} + F_{(EO)} \\ &= \left[K_{p,x} + V_W + \left(\frac{i_d}{z_x f}\right) \times \frac{u_x}{\sum_1^i u_i\, c_i}\right] \times c_x \\ &= [K_{p,x} + V_W] \times c_x + \frac{i_d t_x}{z_x f} \end{aligned} \quad \text{... (Equation 2)}$$

where, $K_{p,x}$ = Permeability coefficient, V_W= Linear velocity of solvent flow, ^{i}d= Current density (current applied per unit area), f= Faraday's constant, u_i and c_i = The mobility and ionic concentration carrying charge across membrane, and u_x, z_x, c_x, t_x = The mobility, valence, concentration and transport number of drug (x), respectively [14, 19].

Devices for Ocular Iontophoresis: Various types of iontophoresis devices and electrodes have been designed for ocular drug delivery, and they mainly differ in dimensions, features, and applications though all of them follow the same transport mechanism as discussed above. Some of the widely used devices are Eyegate® II delivery, OcuPhore® delivery, and visulex™ for ocular drug delivery.

TABLE 2: IONTOPHORESIS DEVICES FOR OCULAR DRUG DELIVERY

S. no.	Device	Innovator	Electrodes	Current Generator	Application
1	EyeGate® II drug delivery 	EyeGate Pharma	An applicator (Eyecup) in which one electrode is placed on eye cavity and other electrode placed at the nearby position of eye (usually placed on forehead).	Direct electric current generator	Transscleral and transcorneal iontophoresis
2	OcuPhore® Hydrogel 	IOMED Inc., USA	An applicator with a patented Ag-Ag chloride ink conductive element and a return electrode at nearby position from the eye (usually placed in backside of ear).	Direct electric current generator	Transscleral iontophoresis commonly
3	Visulex™ 	Aciont® Inc., USA	It consists of a unique membrane that enhances drug permeation and expels the transfer of other ions.	Drug dosing controller	Transscleral iontophoresis
4	Iontofor-CXL 	*Sooft, Italia* S.P.A[20]	It consists of Iontofor-CXL mesh electrode as a reservoir or a hypodermic needle as a return electrode and a vacuum syringe.	Ionto-CXL Power generator	Corneal iontophoresis

EyeGate®-II Drug Delivery: This iontophoresis device has been developed by EyeGate Pharma and used for ocular delivery of various antibacterial, antiviral, anti-metabolites, and steroidal drugs, including the gene therapy. Eyecup or the applicator is made up of an annular shape silicone probe with an internal diameter of 5-10 mm and a different size ranging from 0.4 cm^2 to 0.8 cm^2. The bottom part of the device has a concave shape in order to facilitate its appropriate fitting on the surface of the eye. The drug solution is filled into the applicator, which acts as a reservoir for drugs, and an electrode is dipped or immersed into it. Eyecup is made up of two sections: the first section supplies the drug solution, and the alternative holds the electrode and removes air bubbles that may otherwise disturb the current flow. As a result, a negative pressure is generated, which holds and maintains the applicator in its position. The applicator is placed on the eyeball after applying suitable anesthesia. The charge on the electrode placed inside the eyecup is decided on the basis of charge present on the drug solution. Another electrode is placed at the nearby position of the eye (preferably on the forehead). A constant direct electric current not exceeding 20mA/cm^2 and preferably not exceeding 10mA/cm^2 is applied by a DC generator [2, 21]. EyeGate-II drug delivery has completed Phase-II and Phase-III clinical studies for treating uveitis and dry eye by delivering dexamethasone phosphate solution [2, 22].

OcuPhore® Hydrogel Device: It is an iontophoresis system developed by IOMED Inc. USA, which used a drug saturated gel (drug-loaded hydrogel) as the delivery probe [23, 24]. It consists of a polyacetal sponge or pad which absorbs the drug formulation. This probe is, in turn, connected with a small shell made up of silicon that consists of the patented conductive element or current distribution element (CDE) in Ag-AgCl ink known as the drug applicator. At the time of drug delivery, the pad is

treated by charged drug solution and kept in lower cul-de-sac or lower eyelid of the eye. This complete unit is attached to the DC generator through a flexible wire, and a return electrode is placed below the ear [15].

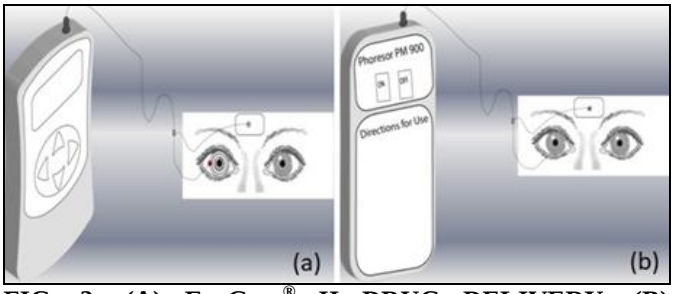


FIG. 3: (A) EyeGate® II DRUG DELIVERY, (B) OcuPhore® DRUG DELIVERY

Modifications in Ocular Iontophoresis: In the past few years, some novel advancements have been done in iontophoresis techniques for enhancement of ocular drug delivery using various types of iontophoretic devices and electrodes. Different devices developed till now vary in either shape or size of applicator for different applications and patient compliance.

A. Eljarrat *et al.*, used a self-designed portable mini-ion device for the corneal ionto-phoresis, which includes drug-loaded hydrogel disk inserted by a cylindrical probe [25].

B. Zhang *et al.*, fabricated a device with polyimide substrate in which an arc-shaped gilded electrode is placed under the eyelid steadily [26].

C. Sarraf *et al.*, used an iontophoresis device consisting of an iontophoresis probe, a micropipette tip, a Y-shaped plastic connector comprising of Ag-AgCl electrode in the side arm and a 1 ml syringe [27].

D. Barza *et al.*, has worked on a modified trans-scleral iontophoretic device which consists of the small central orifice (0.5mm), shorter iontophoretic column with an expansion chamber to trap air bubbles. The electrode is retained in its position by the suction through tuberculin syringe [28].

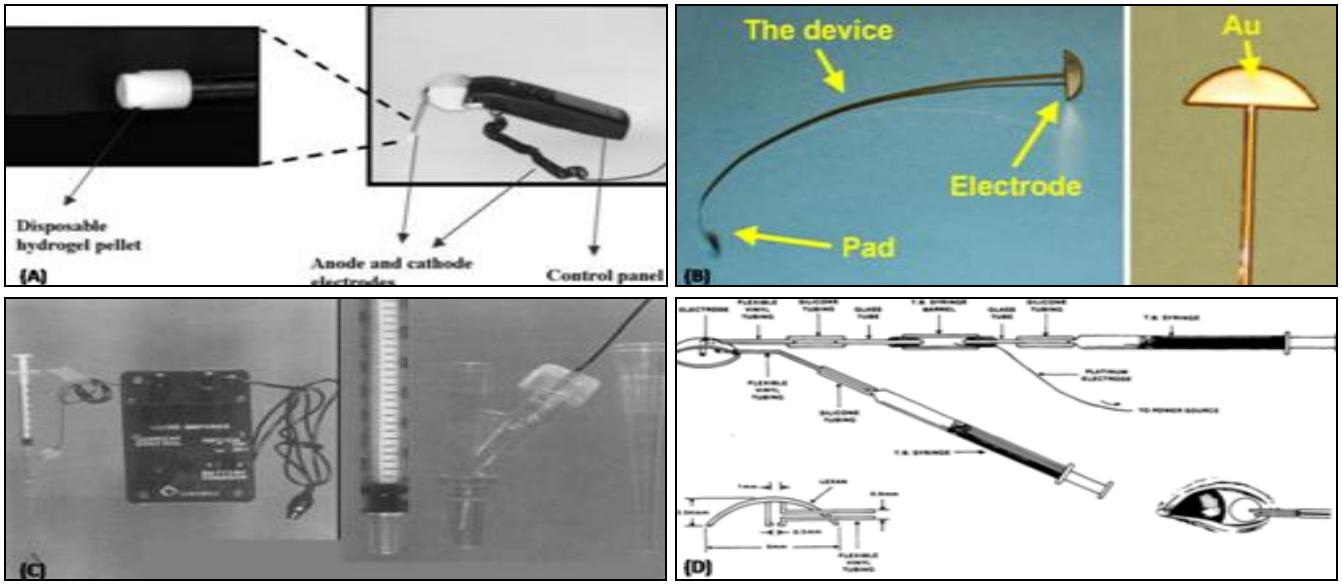
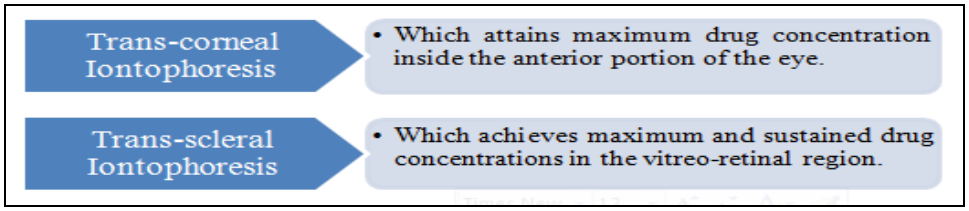


FIG. 4: MODIFICATIONS IN IONTOPHORESIS DEVICES MADE BY (A) ELJARRAT *et al.*, (B) ZHANG *et al.*, (C) SARRAF *et al.*, (D) BARZA *et al.*

Approaches of Ocular Iontophoresis: There are majorly two types of iontophoresis approaches that can be employed for delivery of drugs into the eye, and those are discussed as below [7]:



Trans-corneal Iontophoresis: It is the approach of ocular drug delivery across the corneal membrane wherein excessive concentration of a drug is attained in the anterior portion of the eye which helps in the treatment of various disorders, *i.e.*, glaucoma, corneal ulcers, dry eye syndrome, bacterial keratitis, and eye inflammation because drug delivery to the posterior segment of the eye is not essentially required in most of the cases. As the intraocular injection and surgical implants may lead to bleeding, damage to internal tissues, and inflammation of the eye, whereas frequent injections may cause endophthalmitis, therefore, transcorneal iontophoresis is not only helpful in avoiding these conditions but also avert these conditions to become a serious one.

The transcorneal iontophoretic drug delivery by crosslinking of riboflavin/ ultraviolet A may additionally increase the concentration of drug inside the stroma [29]. Preclinical *in-vivo* studies are performed on animals for evaluating the extent of transcorneal iontophoretic drug delivery, and *in-vitro/ex-vivo* studies are performed on physiological relevant models, *e.g.*, franz diffusion cell [30, 31]. Transcorneal iontophoresis helped in the enhancement of gentamicin permeation across cornea and aqueous humor of the rabbit eye upto 100 fold as compared to topical application onto control eye when observed under same conditions. Hence, transcorneal iontophoresis of antibiotics can be considered as an effective way to treat bacterial keratitis and various ocular infections [32].

Trans-scleral Iontophoresis: It is the approach by which higher drug concentration is achieved in the vitreoretinal or posterior segment of the eye for a prolonged time. The distribution and clearance of macromolecules inside the eye is studied *in-vivo* after transscleral iontophoresis by using magnetic resonance imaging (MRI) [33]. This drug delivery approach has long been used to treat diseases such as uveitis, glaucoma, age-related macular degeneration, and other disorders that may even lead to vision impairment and blindness.

TABLE 3: RECENT RESEARCH ON OCULAR IONTOPHORESIS OF DRUGS

S. no.	Drug	Device	Current (mA) and duration of time (min)	Current Intensity (mA/cm^2)	Formulation	Dose
1	Dexamethasone [18]	Portable iontophoretic device polyacrylic-porous hydrogel	1.5 mA/cm^2 for 4 min	-	Dendrimers	-
2	Gentamicin [19]	Mini-ion device with hydogel disk probe	1.0 mA for 60 sec	5.1	Drug loaded hydrogel	26.11 mg gentamicin sulfate
3	Methotraxate [19]	-	1.0 mA for 2 min	1.6	Drug loaded hydrogel	2.15 mg methotraxate solution
4	Tobramycin [19]	Ocular applicator with plunger of tuberculin syringe	0.8 mA for 5 or 10 min	0.84	Solution	25 mg/ml
5	Ciprofloxacin hydrochloride [30]	-	0.75 mA/cm^2 to 6.25mA/cm^2	-	-	-
6	Aminoglycoside antibiotic amikacin [36]	Ocular applicator and a hydrogel martix	2,3 and 4 mA for 20 sec	-	-	200 mg/ml amikacin solution
7	0.5% solution of sodium iodide [37]	-	0.2 mA for 7 min	-	-	0.5% sodium iodide
8	Cefazolin, ticarcillin, and gentamicin [38]	Ocular applicator with plunger of tuberculin syringe	0.1-2 mA for 1-10 min	-	Solution	94-207 µg/ml
9	Dexamethsone phosphate [39]		0.2 mA	-	Solution	40 mg/ml
10	Acetylsalicylic acid [40]	Microprocessor controlled (CCI)	5 mA for 10 min	5	Solution	10 mg/ml
11	Dexamethasone [44]	Phoresor II Auto, Model PM 850, Iomed, Inc.	2mA for 5 min	-	Solution	0.5µCi/ml

However, transscleral iontophoresis also suffers from disadvantages like it may cause certain complications such as hemorrhagic necrosis of chorioretinal tissues, disruption of retinal construction, fibrosis, and RPE hyperplasia at the site of iontophoresis [34].

Drugs may also be administered through trancorneal or transscleral iontophoresis with the agar solution, *e.g.*, gentamicin sulfate was combined with 2% agar solution because of its low molecular weight, polar nature and lipid insolubility [19]. The corticosteroids, *e.g.*, methyl prednisolone was also administered by transscleral iontophoresis which otherwise shows poor ocular permeation by conventional topical drug administration [35].

TABLE 4: PATENTS ON OCULAR IONTOPHORESIS DEVICES

S. no.	Patent no.	Topic
1	US9700456B2	Device and method for corneal delivery of riboflavin by iontophoresis for the treatment of keratoconus [20]
2	US8452391B2	Ocular iontophoresis device [22]
3	US20020016575A1	Ocular iontophoretic apparatus [24]
4	US6154671A	Device for the intraocular transfer of active product by iontophoresis [41]
5	US793714B2	Irritation-reducing ocular iontophoresis device [42]
6	CA2707964A1	Methods for delivering siRNA via iontophoresis [43]
7	WO2013061350A1	Improved cross-linking composition delivered by iontophoresis, useful for the treatment of keratoconus [44]
8	CA2325428A1	Ocular iontophoretic apparatus handle [45]

CONCLUSION: Ocular iontophoresis is a novel tool for delivering the drug into the eye, across the blood-aqueous as well as blood-retinal barriers by an easy, rapid, and non-invasive manner with enhanced permeation and ocular bioavailability. It is possible to deliver the drug deep inside the eye even to the vitreoretinal region or posterior segment of the eye apart from anterior segment through the trans-corneal or trans-scleral iontophoretic techniques. A better understanding of drug behavior within the eye during electric current application and novel designs of devices, electrodes, and probes specific to the ocular application have resulted in more efficient intra-ocular penetration of drugs using ocular iontophoresis.

The drug of different pharmacological classes, *i.e.*, antibiotic, anti-inflammatory, antiviral, antifungal, antimetabolites, steroidal drugs, even with large molecular size may also be transported through this technique into the eye with better patient compliance and overcoming the drawbacks of conventional delivery systems such as intravitreal and perocular injections. High concentrations of both lipophilic and hydrophilic drugs can be easily penetrated through the ocular barriers, and a rapid therapeutic level can be achieved.

The development of newer drugs for this purpose and/or application of established drugs that could be charged correctly for iontophoresis will help in treating the patients in an effective, controlled, and safe manner without the need for frequent instillation of drops or intraocular injections.

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