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# Review Article

# Advances in Iontophoresis for Drug Delivery

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## Abstract

*Iontophoresis is an exciting technology that was initially investigated 250 years ago. Simply defined, it is the application of an electrical potential that maintains a constant electric current across the skin or barrier that enhances the delivery of ionized as well as unionized moieties. In the past few years, different types of iontophoresis such as transdermal, ophthalmic, transungual, buccal, ural and transnasal iontophoresis have been reported. Each system has its own advantages and drawbacks. The review summarizes recent findings and applications of various iontophoresis techniques.*

***Keywords:*** *Iontophoresis; transdermal; ocular; buccal; transungual; ural; drug delivery.*

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## Introduction

Iontophoresis is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The systemic drug delivery systems often require large dose and are associated with gastrointestinal side effects, while topical application of solutions, suspensions, and ointments show variability in absorption patterns. Iontophoresis technique is capable of expanding the range of compounds that can be delivered through ocular, transdermal, ural, transungual, buccal or by nasal route. One key advantage of iontophoresis is that it offers the possibility of externally controlled flux modulation, carefully adjusted to the needs of the patients[1-4]. Various types of iontophoresis observed are discussed below.

## Ocular Iontophoresis

Delivery of drug to the inner eye still presents a critical problem in ocular therapeutics. Topical administration cannot effectively reach the ocular fluids, where as systemic drug delivery has restricted access due to blood-aqueous and blood-retinal barriers. The retrobulbar and subconjuctival injections do not produce adequate drug levels, while direct intracameral or intravitreal delivery leads to intraocular complications[5]. Ocular iontophoresis could be a solution for such problems.

Ocular iontophoresis was first investigated in 1908 by the German investigator, Wirtz, who passed an electric current through electrolyte-saturated cotton sponges placed over the globe for the treatment of corneal ulcers, keratitis and episcleritis[6]. Basically, in ocular iontophoresis, a donor electrode is placed in the eye while another electrode is placed on the body surface to complete the electrical circuit. The drug to be delivered into the eye is loaded in the donor electrode. An electric field is applied across the eye to enhance the delivery of the drug into the eye[7]. It has been suggested that this technique is relatively easy, convenient for use, safe, and provides fast and higher drug concentration in the specific ocular site, thereby providing solution to the low bioavailability of drugs. It is also well tolerated at low electric current density[8-10]. However, it causes minimum discomfort to patients and is not entirely harmless for ocular tissues[11-12].

Iontophoresis has been evaluated for various drugs into the eye[13-14]. This technique can reproducibly deliver therapeutic concentrations of various ophthalmic drugs, such as corticoids, antibiotics, peptides, and proteins, to both segments of the eye. The drugs can be delivered either by transscleral or transcorneal iontophoresis. Transscleral iontophoresis presents more advantages when compared to transcorneal delivery, owing to scleral larger surface area, enhanced delivery of the drugs to the posterior segment and least possibilities of systemic absorption.

### *Transscleral Iontophoresis*

In phakic animals, the lens-iris diaphragm limits penetration of a topically applied drug to the posterior tissues of the eye, such as the vitreous and retina. Transscleral iontophoresis overcomes this barrier and delivers drugs directly into the vitreous and retina through the choroids[15]. Transscleral iontophoresis of steroids (dexamethasone and methyl prednisolone) can be the alternative treatment for many ocular inflammations. Detailed pharmacokinetic studies have been performed on transscleral iontophoresis for various drugs[16-20]. Every drug resulted with different patterns of distribution in the vitreous. Controlled distribution concentration for 1 to 6 hours into the vitreous chamber has been reported for carboplatin after transceral iontophoresis. A previous study also revealed that the transscleral iontophoretic treatment can be used to obtain high concentrations of drugs to the posterior segments of the eye using a short transscleral iontophoresis with low current, without removing the conjunctiva[21].

Several investigators have conducted clinical studies using transscleral iontophoresis of the anti-inflammatory corticosteroid, methyl-prednisolone hemisuccinate (SoluMedrol). The procedure was safe, well tolerated and easily applied for the treatment of severe ocular inflammation thereby reducing the systemic side effects of corticotherapy[22].

***Transcorneal Iontophoresis***

The transcorneal iontophoresis has demonstrated good results for various investigations. Its application in the treatment of corneal ulcers offers a potentially effective method of management. Gentamicin, tobramycin and ciprofloxacin iontophoresis have resulted in significantly fewer bacterial colonies in the cornea compared with frequent eye-drops instillation[23-26]. Using this method, it has been revealed that after a short iontophoretic treatment of 1 mA for only 1 min with transcorneal iontophoresis of dexame-thasone, a 30 fold higher concen-trations in the cornea (1363.7F 436.3 Ag/g) is achieved when compared with the common treatment of frequent drop instillation every 5 min for 1 hour[27]. Berdugo et al. have used trans-corneal iontophoresis (300 µA for 5 min) to enhance *in vivo* delivery of an AS-ODN against VEGFR-2 using rat cornea. The AS-ODNs penetrated into all corneal layers[28].

In earlier studies[5], the β-blocking agents, timolol maleate and betaxolol hydrochloride, showed significantly increase in permeation through transcorneal iontophoresis. However, iontophoresis does not always show good result for penetration, as iontophoresis of vancomycin, a complex glycopolypeptide antibiotic, has resulted in poor corneal penetration compared with the other antibiotics, due to its high molecular weight (1448 Dalton) that highly influence the effectiveness of the iontophoretic drug delivery[29].

Voigt et al[30] used the combined transcorneoscleral iontophoresis to enhance intraocular penetration of rat antinitric oxide synthase II oligonucleotides (anti-NOSII AS-ODNs) in the rat model of endotoxin-induced uveitis (EIU). The anti-NOSII AS-ODNs were detected intact in all the corneal layers, iris/ciliary body, peripheral retinal layers as well as conjunctiva and sclera 1 hour post-iontophoresis[30].

Preliminary toxicity to the eye after iontophoresis indicated a reversible inflammation with a current intensity of 5.1 mA/cm$^2$ for 2 min. Further, iontophoresis effect on the eye surface was evaluated by histopathology of the corneal tissue 5 min and 8 h after iontophoretic current of 0.5 and 1 mA for 1 and 2 min (2.5 and 5.1 mA/cm$^2$). Minor reversible epithelial defects and stromal edema were found 5 min after the iontophoretic treatment, which disappeared or diminished 8 hours afterwards[27].

## Iontophoretic Devices

Different eye-cup shapes exist[31-35], including an annular shape silicone probe for transscleral iontophoresis (called FEyegate, Optis, France) with a 13 mm opening to avoid contact with the cornea, used by Behar-Cohen[36], Hayden[37] and Voigt[38]. The two approaches for drug retaining in the iontophoretic device are filling an eye cup with the drug solution, while a metal electrode extended from the current supply submerges into the solution. The eye cup has two ports: one delivers the drug solution and the other holds the metal electrode and aspirates air bubbles that can disrupt the current supply, thus creates a slightly negative pressure that maintains the applicator in place. The ground electrode is attached usually to the ear of the animal, as close as possible to the former electrode, to obtain minimal resistance. Another approach is using a drug saturated gel as the delivery probe. This method was first used by were Jones and Maurice[39], who delivered fluorescein into the anterior chamber of the eye using a fluorescein-saturated agar-gel. The gel was placed in a plastic tube and was

partly extruded from the tube to make a direct contact with the eye.

OcuPhor™ hydrogel drug delivery applicators have been studied in 24 male and female subjects[40]. The applicators were well-tolerated and no clinically significant changes in symptomology or in ophthalmic assessments were seen following exposure to 0–3.0 mA for 20 min or 1.5 mA for 40 min. At 4.0 mA 2 of 4 subjects reported a burning sensation[40].

## Transdermal Iontophoresis

Transdermal iontophoresis is the application of an electrical potential that maintains a constant electric current across the skin and enhances the delivery of ionized as well as unionized moieties[41]. It offers various advantages such as easier termination of therapy, better control of drug delivery, improving delivery of polar drugs as well as high molecular weight substances, benefits of bypassing hepatic metabolism and reducing considerably the inter and intra-individual variability[42-43] and ability to be used for systemic delivery or local delivery of drugs.

## Transungual Iontophoresis

Nowadays, persons suffering from nail diseases are growing. Fungal infections in the nail can lead to severe health problems if left untreated in immuno-suppressed individuals[44]**.** Many nail diseases are notoriously difficult to cure owing to the nail barrier and the deep-seated target site underneath the nail plate. Long treatments are usually needed and relapses are common[45]. Oral drug delivery is somewhat successful in treating the nail disorders, but side effects may be severe due to considerable high doses required. Topical monotherapy is considered less efficient in treating nail disorders, such as onychomycosis, due to poor trans-nail bioavailability of drugs[46]. There are two main factors that could limit the accumulation and activity of drugs in the nail on topical application. First, the physicochemical properties of the drug need to be favorable for absorption through nail matrix. The nail matrix is relatively more permeable to polar compounds than nonpolar compounds[47-48]. Second, binding of the drug to keratin reduces the availability of the free drug[49-50]. Water solubility being one of the criteria for drug permeation across the nail, antifungal drugs that are poorly water-soluble do not achieve significant penetration across nail plate. Provided a suitable iontophoretic device could be designed and the electrical protocols are optimized, the transport of not only the ionic drugs but also uncharged drugs could be enhanced across the nail stratums.

The transport of glucose and griseofulvin across the human nail have been studied and the results clearly indicate that the nail plate exhibits iontophoretic permselectivity similar to human skin[51]. At pH > 5, the anodal iontophoretic transport is high due to the net negative charge on the nail plate which attracts the cations. The decrease in the anodal iontophoretic transport of glucose at pH < 5 that is often observed is most likely due to the reversal of net charge present on the nail plate at lower pH. In an another study, Murthy et al[51] reported that salicyclic acid delivery across human nail, where the increase in the current density directly increases the number of ions moving across the barrier. Other factors which affects the delivery are the pH and drug concentration[52].

Griseofulvin is a sparingly water-soluble antifungal drug with log P of 2.0[53]. Therefore its ability to permeate into hydrophilic keratinous nail plate is limited. The transport of griseofulvin could be enhanced ~8 fold by iontophoresis. The iontophoresis enhanced transport of prednisolone sodium phosphate across the thumb nail has been reported[54-55].

## Buccal Iontophoresis

Buccal administration of drugs is advantageous for those drugs that encounter degradation in the gastrointestinal tract or

severe hepatic first-pass metabolism and require the administration of large doses to reach effective therapeutic levels in the target site[56-57]. Side effects are minimized. Among the epithelial tissues, the buccal mucosa offers good performance for local/systemic pharmacological actions because of its permeability. Since a major limitation in the development of a buccal drug delivery device could be the low permeability of the buccal mucosa, because of relatively small surface area available for absorption and poor retention of the drug and/or drug formulation at the site of absorption. The drug passively crosses the membrane whereas the application of electric fields promotes drug diffusion[58]. The application of a current density of 1 mA/cm2 or more determines a good improvement[59].

Jette Jacobsen's work showed that the iontophoretic approach was feasible to enhance and control the rate of buccal drug delivery of atenolol hydrochloride, and iontophoretic enhancement ratios valued above 100 were obtained. However, an 8 hour treatment period employing iontophoresis resulted in disordering of the outer epithelial cell layers[60]. No sign of flogosis was found in any of mucosal specimens treated. The cells appeared vacuolated due to the presence of intracytoplasmic material, which is likely ascribable to drug accumulated. No severe cytopathic effects were found in any mucosal specimen treated with the lowest applied current density.

## Transnasal Iontophoresis

The delivery of the drugs to the brain is a challenge, as systemically administered drugs fails to pass through the blood brain barrier to enter the brain. A great deal of efforts has been invested in developing the ways to open or defeat the blood brain barrier in order to deliver drugs from blood to the brain. Direct nose to brain delivery of small molecules, peptides and proteins are well known phenomenon. Transnasal iontophoresis is another technique in the field of drug delivery to the brain.

Lerner et al[61] studied the transnasal iontophoresis of octreotide in rabbits. He placed electrodes containing a drug reservoir into the deep nasal cavity with a return electrode placed at the back of head. The current strength, 3 mA, was applied for 60 min. The experiments resulted to elevated levels of octreotide in brain, with varying results due to electrode and tissue damage during insertion of electrode.

## Ural Iontophoresis

Iontophoresis improves the tissue penetration of locally applied drugs. Thus, high local drug tissue levels can be achieved without general side effects. Canine[62] studied iontophoresis using a specialized urethral catheter delivery system, equipped with an iontophoresis electrode and showed that it could safely deliver lidocaine to the prostate without a significant increase in serum levels. Possible applications in urology in addition to local anesthesia such as delivery of antibiotics for prostatitis, chemotherapy for prostate and bladder cancer, gene therapy, and prostate enzymatic ablation for benign prostate hyperplasia were also suggested. This exciting technology could certainly play a significant role in future[62].

## Patient Related Consideration

### *Neonates*

Continuous monitoring of preterm infants is a critical care issue. However, 'minimal handling' is also recommended[63] since each medical intervention on a premature neonate increases the risk of infection, and amplifies thermal and energetic losses. In addition, conventional monitoring by blood sampling (i.e. plasma or serum) constitutes a painful and difficult procedure; not only is it difficult to find a vein from which to sample, but severe bruising and/or scarring of the

immature skin can also result[64]. Furthermore, preterm neonates have a very limited blood volume.

Indeed, premature neonatal skin provides a unique portal for noninvasive transdermal monitoring by iontophoresis because the underdevelopment of the stratum corneum permits significantly increased drug permeability. To date, various applications have been envisaged for both drug monitoring (e.g. clonidine and theophylline[65]) and diagnostic purposes (e.g. phenylalanine[66], lactate[67]). Additional efforts to improve the extraction efficiency have been undertaken[68-69].

### *Paediatrics*

This iontophoresis system seems to provide a well tolerated method for providing dermal anesthesia with lidocaine in children that is not associated with the systemic delivery of this drug[70]. Several studies have reported findings on the ultrastructure of stratum corneum after iontophoresis. Low current densities did not affect the structure of stratum corneum sheets; however, increased current densities, resulted in a number of changes to the lipid organization, suggesting that the electric field can perturb the intercellular lamellar ordering in the stratum corneum[71]. Fatouros et al. reported that 9 hour application of a 0.5 mA/cm2 current *in vitro* and 3 hour 0.25 mA/cm2 *in vivo* did not affect the skin architecture dramatically and that as far as structural changes in stratum corneum are concerned iontophoresis is a safe method[72]. It has been demonstrated that iontophoresis only leads to very mild skin erythema and edema[73].

## Clinical Applications

### *Anaesthetics delivery*

Delivery of anaesthetic agent during dermal surgery is the widest application of iontophoresis. The topical delivery of lidocaine for providing local anesthesia prior to tooth extraction or root canal surgery by iontophoresis was reported by Gangarosa[74].

### *Pain management*

Opioid analgesics have low molecular weights (300-500Da), usually positively charged and often requires low dose, usually in nanogram, to induce pharmacological effect. The physicochemical and pharmacological properties make these molecules suitable candidates for iontophoretic delivery[75]. Examples of such drugs investigated are fentanyl and sufetanil. NSAID may cause serious adverse effects on the gastrointestinal tract, leading to ulceration and bleeding. Therefore local administration could be an desirable option. Diclofenac sodium[76-81], piroxicam[82-83]have been investigated.

### *Glucose monitoring and insulin delivery*

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. This property, in combination with *in situ* glucose sensors, has been used in GlucoWatch Biographer (Cygnus Inc., Redwood City, CA, USA)[84]. This device allows noninvasive extraction of glucose across the skin, allowing a diabetic's glycemia to be evaluated every 10 min over several hours. Initial clinical trials using iontophoresis of soluble insulin were unsuccessful[85]. Transdermal delivery of insulin by iontophoresis has been accomplished in laboratory animals. In a study of diabetic rats, iontophoretic delivery of bovine insulin affected glucose levels. By contrast, iontophoretic delivery of a monomeric human insulin analogue produced a significant fall in plasma glucose in the rats[86-87].

***Skin cancer***

The treatment of skin cancers by radiotherapy is usually associated with many complications. Iontophoresis could be a solution for such complications. Chang et al[88] investigated the iontophoresis of cisplatin in the therapy of basal and squamous cell carcinomas in the skin and concluded that small lesions would respond best by iontophoresis. Vinblastine subcutaneous administration leads to necrosis and phlebitis, hence not recommended. Also, intralesional administration causes pain and reduces patient compliance. Smith et al [89] investigated the iontophoresis of vinblastine sulfate to treat cutaneous lesions associated with Kaposi sarcoma. All the patients showed significant clearing of their lesions.

***Antiemetic drug delivery***

Jadoul et al[90] conducted iontophoresis study using hairless rat skin to improve the domperidone delivery. A total of 6 hour iontophoresis resulted in 15 fold improvement in drug delivery.

***Antiviral agents***

Azidothymidine, an antiviral agent, has been investigated by different groups[91-92]. This antiviral agent undergoes first pass hepatic metabolism after oral administration, resulting in bioavailability of approximately 60-70%. In addition, drugs having short plasma half-life of approximately 1 hour, often requires maintenance of blood levels. Oh el al[91] investigated iontophoretic delivery of azidothymidine and reports an approximately 1.5-fold increase in the cumulative amount of azidothymidine delivered iontophoretically from solution over 24 hour.

***Cardiovascular agents***

Various studies have been conducted on cardiovascular drugs including antihypertensive drugs (calcium channel blockers and β-adrenoreceptor blockers)[93-105]. The iontophoretic delivery of metoprolol using rabbit model has been investigated. Arterial pressure was induced by intravenous administration of methoxamine hydrochloride at the rate of 30 $mgkg^{-1}min^{-1}$ for 2 hours. High frequency pulsed iontophoresis (50 kHz, 30% duty cycle) at a current density of 0.08 mA $cm^{-2}$ was begun 15 min after onset of the IV infusion. The metoprolol iontophoresis significantly decreased the systolic blood pressure from 126±9 to 86±1 mmHg and diastolic pressure from 99±7 to 72±10 mmHg[106].

***Dermatologic applications***

*Treatment of hyperhydrosis*

The most successful application of iontophoresis is for the treatment of hyperhydrosis. The basis for such treatment and its practical aspects have been well described[107-109]. Yamashita et al[110] studied the efficacy of iontophoretic delivery of calcium for treating hydrofluoric acid-induced burns. They observed that burn areas were significantly reduced by iontophoresis more than any other mode of calcium administration, and iontophoresis was more efficacious than topical or injection therapy for experimental hydrofluoric acid burns.

*Fungal infections*

There are reports of the successful treatment of dermatophytosis with the use of copper sulfate iontophoresis[111] and of sporotrichosis with potassium iodide iontophoresis[112].

*Ischemic leg ulcers*

Iontophoresis has been used for the treatment of patients with ischemic leg ulcers. The effect of histamine iontophoresis on ulcers was studied by Abramson et al [113], complete healing was reported in four of the five patients.

*Cosmetics*

Most recently, a new generation of iontophoretic patches, containing a fully integrated power source, has become available for home use. The patches are enabled through the invention of proprietary thin and flexible, safe and non-toxic, fully disposable electrical power cells and microelectronics incorporated into a simple cosmetic patch. The developer, has revealed two types of iontophoretic patches. Type one boosts the topical delivery of lotions, gels, serum preparations and other cosmetic formulations. The other type provides immediate effects of wrinkle reduction and skin smoothening. The patches can be designed to suit and target any area of the body[114].

*Anti-wrinkle effects*

Human clinical studies on dozens of subjects have shown that a single 20-minute treatment using the patch results in a visible reduction of the number and depth of wrinkles under the eye and at the crow feet's area.

*Treatment of pigmentation disorders*

Vitamin C is known to both inhibit melanin formation and reduce oxidized melanin. However, vitamin C does not easily penetrate the skin. In 2003, Huh et al[115] reported that iontophoresis treatment using an active form of vitamin C (namely magnesium ascorbyl phosphate or MAP) at 3.6% for 12 weeks resulted in significant reduction of pigmentation.

*Treatment of scars*

In 2002, Schmidt et al[116] reported on treatment of post-acne scars using iontophoresis with 0.025% tretinoin gel. At the end of treatment, in 94% of patients a significant decrease in the scar depth was observed clinically. In conclusion, tretinoin iontophoresis was found to be effective, noninvasive treatment of atrophic acne scars without causing disturbing side effects.

*Peyronie's disease treatment*

In the practice of urology, the primary use for iontophoresis has been for the treatment of Peyronie's disease (PD). PD is characterized by the clinical symptoms of diseases is initial penile pain followed by development of plaque, penile deviation, plaque calcification, penile deformation and erectile dysfunction. The majority of patients initially prefer conservative treatment. Indication for conservative therapy seems to be the early painful and progressive stage of the disease[117].

The surgical correction is the treatment of choice for major penile angulation and deformation, A variety of medical regimens have been used to resolve pain, plaques and minor deviation. Oral vitamin E, potassium para-aminobenzoate and tamoxifen, and intralesional injection of steroids, orgotein, collagenase, verapamil and interferon-a have shown differing grades of efficacy to reduce the symptoms of PD. However, except for vitamin E, they have considerable side effects, such as gastrointestinal symptoms, which often leads to premature termination of para-aminobenzoate therapy. Local injections are extremely painful and require local anesthesia.

Iontophoretic therapy for PD have been tried in three patients. The treatment consisted of three, 20-minute sessions weekly for two weeks with 1% cortisone cream applied directly over the penile plaque. A positive electrode was placed above the application site of cortisone cream and a negative electrode was placed at a neutral site (eg. thighs, abdominal wall). A current of 3 ± 5 mA was applied, depending upon the patient's tolerance. These three patients were successfully treated with iontophoresis in spite of having mature PD[118]. It was demonstrated that a substance, such as verapamil, could be detected in PD plaques

after iontophoresis[119]. In the controlled study, a response was observed by reduction of plaque size in 100%, on curvature in 57%, and on pain in 76%. Improvement in sexual function was observed in 51%[120].

Riedl et al[121] used the self adhesive iontophoretic patch in the treatment of PD and reported that iontophoresis of dexamethasone, lidocaine and verapamil is effective for peyronie's disease and especially beneficial for painful lesions of less than 12 months in duration and for deviations less than 60 degrees. In their opinion, this procedure should be regarded as first line noninvasive therapy for PD[121]. Thus, iontophoresis presents a potential area of development for drug delivery in patients with PD and other penile disorders.

## Conclusion

The iontophoretic field of drug delivery technology holds the promise of delivering the technology breakthrough and is moving very fast from concept to reality. Some pharmaceutical companies are also set to launch major initiatives in this direction. This technology will attract attraction in the consumer market.

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