Expert Opinion

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Iontophoretic drug delivery using the IOMED Phoresor® system

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Iontophoresis, or electromotive drug administration, is a process that enhances the delivery of drugs through a biological membrane via the application of low-intensity electrical current. This technology offers several advantages over oral and injection drug delivery. Key advantages of iontophoretic drug delivery include the avoidance of pain and potential for infection associated with needle injection, the ability to control the rate of drug delivery, the ability to programme the drug-delivery profile and the minimisation of local tissue trauma. Research using iontophoresis has shown delivery of a number of drug classes. By controlling the applied electric current one can tailor a dosage regimen with a drug delivery profile specific for an indication and the needs of the patient. Advances in iontophoretic electrode design, microelectronics and methods to optimise iontophoretic drug delivery have improved the ability to safely deliver both older, off-patent drugs, as well as new chemical entities being developed to treat a variety of diseases. In addition to transdermal applications, current research indicates that iontophoresis may prove to be a viable noninvasive drug delivery method for treating conditions that affect the back of the eye.

Keywords: active drug delivery, IOMED, iontophoresis, noninvasive, ophthalmic, programmable drug delivery, transdermal

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1. Introduction

Iontophoresis has been used since 1900 when Leduc [1] demonstrated the potential of this procedure with experiments showing rabbits suffering fatal seizures minutes after transcutaneous iontophoretic delivery of strychnine. A constant current of 40 – 50 mA was applied in two rabbits connected in series. Strychnine sulphate (positive ion) was introduced into the first rabbit by connection to a positive electrode (anode), and potassium cyanide (negative ion) was given to a second rabbit via the negative electrode (cathode). Both rabbits died due to strychnine and cyanide poisoning, respectively. To confirm the phenomenon, Leduc reversed the two delivery electrodes (anode used to deliver cyanide and the cathode for strychnine). Both rabbits survived this experiment.

IOMED, Inc. pioneered the development, manufacture and sale of iontophoretic delivery systems most commonly used to treat local inflammation in the sports, occupational medicine and physical therapy markets. IOMED's active drug delivery systems are a noninvasive method of enhancing and controlling the local delivery of water-soluble ionic drugs into and through the skin and other body tissues using low-level electric current. Commercial products are designed around the proprietary Phoresor® system, which is a reusable microprocessor-controlled electric power supply (dose controller). Single use, disposable active transdermal electrode patches used with the Phoresor system include Iogel®, TransQ®, OptimA®, Anestrode® kits and, most recently, an integrated Companion 80® system.

These delivery devices, when not specifically packaged with drug, are approved under the US FDA's Premarket Notification or 510k medical device approval. Iontocaine®, IOMED's brand of lidocaine HCl 2% and epinephrine 1:100,000 topical

Table 1. Examples of compounds delivered via iontophoresis.

Compound	Polarity	Solution	Purpose/condition	Ref.
Acetic acid	-	2 – 5% acetic acid solution	Calcium deposits, calcified tendonitis	[75-77]
Alniditan	+		Migraine	[78]
Atropine sulphate	+	0.001 – 0.01% solution	Hyperhidrosis	[36]
Calcium	+	2% calcium chloride solution	Myopathy, myospasm, frozen joints	[79]
Chloride	-	2% sodium chloride solution	Sclerolytic scar tissue, adhesions, keloids	[80,81]
Dexamethasone	-	Dexamethasone sodium phosphate 4 mg/ml	Tendonitis, bursitis, arthritis, tenosynovitis Peyronies Disease	[28-34]
Diclofenac	-		Inflammation, pain control	[82]
Fentanyl	+		Pain control	[83-85]
Gentamicin sulphate	+	8 mg/ml	Ear chondritis	[86]
Glucose	+/-		Glucose monitoring via extraction	[45]
Glycopyrronium bromide	+	0.05% solution	Hyperhidrosis	[35,36]
Human parathyroid hormone	+		Osteoporosis	[87]
Hydromorphone	+		Pain control	[88]
Idoxuridine	-	0.1% solution	Herpes simplex	[89-91]
Iodine	-	Iodex ointment	Sclerolytic, antimicrobial, fibrosis, adhesions, scar tissue, trigger finger	[92]
Lidocaine	+	4% lidocaine with or without epinephrine	Skin anaesthesia, trigeminal neuralgia	[16-25]
Lithium	+	2% lithium chloride solution	Gouty arthritis	[93]
Meladinine	-	1% solution of sodium salt	Vitiligo	[94]
Methotrexate	-		Psoriasis	[95]
Morphine	+		Pain control	[96]
Penicillin	-		Infected burn wounds	[97,98]
Pilocarpine	+		Sweat test (cystic fibrosis)	[43,44]
Piroxicam	-		Pain control	[99]
Poldine methyl sulphate	-	0.05 – 0.5% solution	Hyperhidrosis	[38,41]
Potassium iodide	-	10% solution	Scar tissue	[100]
Salicylate	-	2% sodium salicylate solution	Analgesic, sclerolytic, plantar warts, scar tissue, myalgias	[101]
Silver	+		Chronic osteomyelitis	[102,103]
Vincristine Vinblastine	+	Vincristine: 0.01% solution in 9% saline + 5% DMSO	Reduce congestion, postherpetic neuralgia, trigeminal neuralgia	[27]
Tap water	+/-		Palmar, plantar, axillary hyperhidrosis	[35-41,104]
Zinc	+	20% zinc oxide (suspension)	Antiseptic, ulcers, dermatitis, wounds	[105]

DMSO: Dimethyl sulfoxide.

solution was approved by the FDA in December 1995 under a new drug application (NDA) for local dermal anaesthesia. This was the first FDA-approved drug labelled for use with an iontophoresis device.

The advantages of iontophoresis include localised drug delivery in higher concentrations than passive delivery mechanisms, the capability to minimise systemic exposure, which includes bypassing hepatic first pass metabolism, controlled delivery of drugs with short biological half-lifes, increased patient compliance and ease of terminating drug delivery [2-4]. Other advantages include:

- noninvasive drug delivery, which minimises the chance of infection and the biohazard issues associated with needle injections

- ability to provide site-specific drug delivery to avoid systemic side effects
- rapid onset and cessation kinetics
- programmable, controlled and titratable drug-delivery capabilities
- enhanced delivery for a broad range of compounds
- ability to deliver hydrophilic ionic drugs

Over the last few decades, numerous compounds have been studied using iontophoresis; some examples for various transdermal applications are listed in **Table 1**.

2. Market overview

Iontophoretic drug delivery systems are currently used in most of the 28,000 physical and occupational therapy and sports medicine clinics nationwide. It is estimated that on average there are ~ 20,000 iontophoresis treatments administered every day to treat acute local inflammatory conditions in this market. The total iontophoresis market in physical therapy and rehabilitative medicine is currently at ~ $35 million with single digit annual growth. In a study of time missed from work as a result of acute soft tissue inflammation-related injuries (carpal tunnel syndrome, epicondylitis, DeQuervain's tendonitis and plantar fascilitis), > 1 million employees miss work at a cost to the US of $45 billion – $54 billion per year. So far, the greatest portion of this market is captured from the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors.

Iontophoresis is particularly well suited for treating acute pain. Because iontophoresis has the capability of providing on-demand patient controlled drug delivery for breakthrough pain, this is an area targeted for growth. The Alza Corporation (subsidiary of Johnson & Johnson) received an approvable letter from the FDA in July 2004. The Alza delivery system was designed to provide systemic delivery of fentanyl HCl to manage postoperative pain.

Currently, the most common delivery method for topical anaesthetics, other than injection, are lidocaine patches, which have a projected compound annual growth rate of 21.4% for the period of 2003 – 2008 [5]. Lidocaine patches currently compete with anaesthetic creams. It is estimated that the worldwide market for the topical anaesthetic EMLA® Cream sold by AstraZeneca is > $45 million. IOMED believes that its Numby Stuff® product offers a faster, more efficacious alternative to both passive patch and topical cream delivery of lidocaine. Numby Stuff is currently sold primarily into the paediatric market for use prior to shaved biopsies or the placement of vascular access devices. The Joint Commission on Accreditation of Healthcare Organizations has set standards for all healthcare providers to assess and manage patients' pain, and the Occupational Safety and Health Administration has issued new regulations pursuant to the recently enacted Needle Stick Safety and Prevention Act. These standards and regulations provide opportunities to stimulate growth in this market. However, given cost and time constraints in today's healthcare environment, the biggest challenge to Numby Stuff are healthcare providers taking the time to give patients a painless alternative to a lidocaine injection.

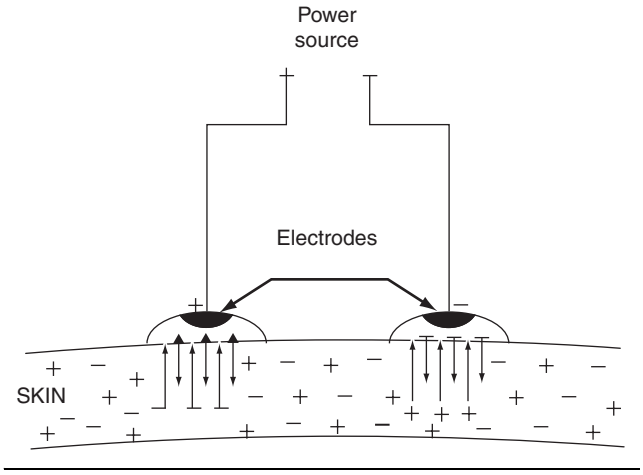

Figure 1. Iontophoresis illustration.

3. Basic principles of iontophoresis

Iontophoresis is the movement of ions driven through a barrier by an electric current. Iontophoresis is based on elementary principles of electricity, which state that like charges repel and opposite charges attract each other (**Figure 1**). When using iontophoresis, the drug is integrated with or added to an electrode (drug patch) that will possess the same charge as the drug, while a dispersive electrode (grounding patch) will carry the opposite charge. The drug ions serve as the ionic conductor of the electrical current typically delivered in milliamps (mA) from the drug electrode into the tissue treatment site. For example, to deliver a negatively charged compound across a biological membrane, the compound is placed under the negative electrode where the compound ions are repelled or pushed through the membrane. The reverse applies to positively charged compounds.

Basic laws of physics and chemistry such as Ohm's law, Faraday's law and Coulomb's law are frequently referred to when explaining important parameters involved in iontophoretic drug transport.

Ohm's law:

$$V = IR$$

Where V is the electromotive force measured in volts, I is the current in amperes (A) and R is the resistance in ohms. At constant voltage, any change in resistance results in a change in the current. With iontophoresis *in vivo*, membrane resistance

decreases during the procedure, which results in an increase in current. These current changes are easily controlled by the microprocessor built into commercial dose controllers (e.g., IOMED's Phoresor system).

Faraday's law:

$$D = \frac{ITMW}{[Z]F}$$

Where D is the drug molecule in gram equivalents, I is the current in Amps, T is the time in sec, MW is the formula weight in g/mole of the drug, Z is the valence or charge of the ionic species and F is Faraday's constant (the transport of one molar concentration of a univalent ion requires the passage of 96,485 coulombs of electricity expressed in coulombs/mole). This equation provides a basis for the premise that the more current applied or the longer the duration (time) of current application, the more ions are moved through the tissue. This equation assumes 100% of the current is carried by the drug ions, which is never the case in commercial drug formulations. To predict iontophoretic drug flux, the fraction of the current carried by the drug must be known.

4. Factors influencing iontophoretic drug delivery

Although the fundamentals of iontophoresis have been understood for decades, advances in electronics, materials science and electrochemistry have only recently rendered the technology commercially practicable as a safe and reproducible means of delivering drugs. These advances have led to the development of more efficient and adaptable drug electrodes, and more reliable, compact and programmable dose controllers. The predominant factors that affect iontophoretic drug delivery include physiochemical properties of the compound (molecular size, ionic charge, concentration), drug formulation parameters such as the diluent/buffer used in the formulation (which can contribute to the presence of competing ions), current density, treatment duration, constant current versus pulsed current and the electrochemistry of the electrode [2,3]. These factors are briefly discussed in this section. More detailed information on factors affecting drug flux with iontophoretic delivery can be found in a recent review article by Kalia *et al.* [6].

4.1 Drug molecular size

Yoshida *et al.* [7] showed the permeability coefficients for a number of positively charged, negatively charged and uncharged solutes across excised human skin were a function of molecular size. In general, as the size of the molecule being transported increases, the permeability coefficient for that molecule across a membrane decreases [7,8].

4.2 Ionic charge

Iontophoresis uses an electrical current to push a drug of like charge through a membrane; therefore, the molecule being transported across the membrane must be in an ionised state with either a positive or negative charge. Non-ionic compounds may also be transported across membranes via iontophoresis if a charge can be incorporated onto the molecule by adsorption of the drug onto an ionic carrier or via electro-osmosis.

4.3 Drug concentration

The Nernst–Planck equation is often used to describe the membrane transport of ions under an electric field.

$$J = (-D)\frac{dC}{dx} + \frac{DzeEC}{kT}$$

Where J is the flux of ions across a membrane, D is the diffusion coefficient, dC/dx is the concentration gradient over the distance x, C is the concentration of ions with the valence z and an electron charge e, E is the electric field over the membrane, k is Boltzmann's constant (1.38054 JK^{-1}) and T is the absolute temperature (273.15°K).

The Nernst–Plank equation indicates that when a concentration gradient and an electric field exist together, the ionic flux is a linear sum of the fluxes that would result from each effect alone. From this equation, an increase in drug concentration will yield an increase in drug flux; however, there are many factors that can cause different experimental results, not the least of which include the complex heterogeneous membranes of human tissue.

4.4 pH

The optimum pH for iontophoretic delivery is where the drug compound exists predominantly in the ionised form. Where a drug's degree of ionisation is strongly pH-dependent, care must be taken in formulating the drug diluent. Gangarosa [9] and Siddiqui [10,11] have demonstrated the importance of pH in the enhancement of solute transport by iontophoresis. The hydrochloride salt of a local anaesthetic was optimally delivered via iontophoresis at a pH of 5; increasing solution pH converted the positively charged hydrochloride to a nonionised state. pH changes are especially significant when considering protein and peptide drugs, because the pH of solution generally determines the charge on these molecules; pH may also influence molecular size and shape through aggregation, which can affect transport. Practical acidic and basic pH limits must be considered to avoid damage to tissue underlying the drug delivery electrode.

Electrochemistry at the electrode during iontophoresis must be controlled to prevent undesirable pH shifts due to the hydrolysis of water, which is seen with platinum, zinc, aluminium, carbon and other inert electrodes. Iontophoresis systems using silver/silver chloride conductive components

control the hydrolysis of water and subsequent pH shifts [201]. At the anode, silver oxidises and reacts with chloride to form insoluble silver chloride; at the cathode, silver chloride is reduced to free silver. These reactions are occurring at a lower potential than the hydrolysis of water.

Anode (+) $Ag - e^- \rightarrow Ag^+ + e^-$ | $2H_2O \rightarrow 4H^+ + O_2 + 4e^-$
oxidation $Ag^+ + Cl^- \rightarrow AgCl$ |

Cathode (-) $AgCl + e^- \rightarrow Ag + Cl^-$ | $2H_2O + 2e^- \rightarrow 2OH^- + H_2$
reduction

If using silver as a conductor in anodal drug delivery, one must calculate that a sufficient amount of Cl^- ions will be present in the electrode reservoir to precipitate the Ag^+ ions as AgCl. If not considered, the Ag^+ ions will migrate into and through the drug reservoir into the tissue. This can hinder the transport of cationic drugs and migrating Ag^+ ions can leave a residue or stain the underlying tissue.

4.5 Competing ions

The pH of drug solutions is often controlled by the addition of buffering agents. The use of these buffers along with the addition of other excipients such as preservatives, antioxidants, stabilisers or enhancers add co-ions or competing ions (ion of like charge, but a different type or species) and counter-ions (ions of opposite charge), which are often smaller and more mobile than the drug being delivered iontophoretically. This mix of co-ions and counter-ions reduce the fraction of current carried by the drug ions and result in a reduction of iontophoretic flux of the drug. Bellantone *et al.* [12] showed that competing ions reduced benzoate flux by 50% when an approximately equimolar amount of sodium chloride was added to the donor electrode. For these reasons it is recommended that buffers and other excipients should be minimised in iontophoresis formulations and excipients should be selected that possess ions of low mobility or conductivity.

4.6 Current level

Iontophoretic dosage is controlled by current level (mA) and time (min) and is expressed as milliampere minutes (mA-min). This follows Coulomb's law where Q is the electric force, I equals current in milliamperes and T is time in minutes (Q = IT). Current levels are limited by patient comfort and safety. Although a linear relationship between current and drug flux has long been observed for a wide range of compounds [4], the response can plateau at higher current levels. Once this level has been reached, there are no significant increases in drug flux with further increases in current.

4.7 Continuous versus pulsed current

Lawler *et al.* [13] showed that in skin tissue the continuous use of direct current (DC) sometimes resulted in a polarisation effect, which could reduce the efficiency of iontophoretic delivery proportional to the length of time DC current is applied. This polarised current 'build-up' can be overcome with pulsed DC current [14]. It is theorised that during the 'off' portion of the pulsed cycle, the skin polarisation returns to its near initial electric condition. Pulsed frequency selection is important because enhanced skin polarisation can decrease the efficiency of transport if the frequency is high [15].

4.8 Electrochemistry

Electrochemical stability of the drug during iontophoresis must be considered when determining the suitability of an iontophoretic drug-delivery device. If as a result of the iontophoresis process the active ingredient (drug) undergoes oxidation or reduction, degradation products may compete with the delivery of the active drug moiety if they have the same charge. In addition, electrochemical stability of the drug and any matrix used that contains the drug must be understood to ensure degradation products are not ineffective and/or toxic. This also holds true for excipients; therefore, the electrochemical properties of inactive ingredients should not be neglected.

In summary, many factors affect the safety and efficiency of iontophoretic drug transport. For a given drug formulation, controlling the current density can have a significant influence on iontophoretic delivery. The drug formulation must be optimised to insure drug concentration provides desirable flux. The choice of buffers and inactive ingredients should be selected to minimise competing ions. The pH of the solution should be formulated to maximise ionisation of the active ingredient, and electrode design should ideally prevent the hydrolysis of water and any subsequent pH shifts during the iontophoresis cycle.

5. Iontophoresis devices and procedure

Conventional iontophoresis delivery systems consist of a microprocessor that produces a controlled, direct current stimulus, a drug-delivery electrode and a dispersive (ground) electrode. The most prominent manufacturers of iontophoretic delivery systems are listed in **Table 2**.

The electrodes are commonly connected to the microprocessor by lead wires; however, newer systems are self-contained integrated devices. Iontophoretic drug delivery is a relatively simple procedure and entails placement of the drug delivery electrode (which contains the drug compound) over the area to be treated. The dispersive electrode acts as a ground and is placed on the skin away from the delivery electrode. The dosage and current amplitude are set on the microprocessor dose controller. The total dosage of ions transported across a membrane in iontophoresis is measured in units mA-min, which is an expression of the product of the current used and the duration of delivery time. Mild DC electricity (maximum of 4 mA) is commonly used. A typical iontophoretic drug delivery dose is 40 – 80 mA-min (10 – 20 min at 4 mA, respectively); however, dosage varies according to drug used, clinical indication and patient requirements.

Table 2. Companies that manufacture iontophoresis systems.

Company	Address	Comments	Ref.
IOMED, Inc.	2441 South 3850 West Salt Lake City, UT 84120, USA +1 (800) 621-3347	Manufactures a number of systems for transdermal drug delivery: Numby® for local dermal anaesthesia with NDA for lidocaine/epinephrine Iogel® and the TransQ® product lines OcuPhor® ophthalmic delivery system in preclinical development	[301]
Vyteris, Inc.	13-01 Pollitt Drive, Fair Lawn, NJ 07410, USA +1 (201) 703-2299	Recently approved Lidosite® for local dermal anaesthesia with lidocaine/epinephrine. Not commercially available at the time of this writing	[302]
Alza, Corp.	1900 Charleston Road, Mountain View, CA 94039, USA +1 (650) 564-5000	Approvable letter for IONSYS® system to deliver fentanyl HCl	[303]
Empi	599 Cardigan Road, St. Paul, MN 55126-4099, USA +1 (800) 328-2536	Manufactures the Dupel® transdermal iontophoresis system	[304]

NDA: New drug application.

6. Clinical applications using iontophoretic drug delivery

The ability to achieve surface local anaesthesia has promoted the use of iontophoresis in a multitude of clinical settings. Iontophoresis of lidocaine in combination with epinephrine has been used to achieve local anaesthesia of the skin for patients undergoing venipunctures and minor dermatological procedures [16-25]. In myringotomy, iontophoresis has been a preferred method for obtaining local anaesthesia of the tympanic membrane [26]. Patients with postherpetic neuralgia have received various drugs via iontophoresis for the management of chronic pain [27]. Steroids and nonsteroidal anti-inflammatory drugs have been delivered via iontophoresis in patients with inflammatory musculoskeletal disorders [28-34].

Numerous other applications exist in diagnostics, antineoplastic therapy and antiviral therapy. Iontophoresis with tap water or anticholinergic compounds have been used for the treatment of patients with palmoplantar hyperhidrosis, a condition of excessive sweating in the palms or plantar surfaces [35-42]. Iontophoresis is a preferred method for the delivery of pilocarpine in a diagnostic test for cystic fibrosis [43,44]. Recently, the technology has also served as a platform in the development of blood glucose monitoring devices that utilise 'reverse iontophoresis' to draw glucose through the skin [45].

6.1 Acute local inflammation

As mentioned previously in this article, iontophoresis devices are approved under FDA Premarket Notification 510k medical device allowances when not specifically packaged with drug. Iontophoresis is used extensively by physical therapists (prescription only) and has been clinically administered in > 20 million patient treatments for the delivery of corticosteroids. Of these treatments > 15 million have occurred since 1990, when advancements in electrode technology made by IOMED led to the introduction of its present family of hydrogel patches for use with its microprocessor dose controllers. IOMED's products are used for site-specific corticosteroid therapy to treat acute local inflammatory conditions resulting from exercise, sports injuries, trauma or repetitive motion disorders. The most common of these injuries include tendonitis, bursitis, carpal tunnel syndrome and epicondylitis.

Five published randomised, placebo-controlled studies involving 203 subjects compared iontophoresis of dexamethasone sodium phosphate versus iontophoresis of a placebo [31-34]. Diagnoses included acute lateral and medial epicondylitis, plantar fasciitis, rheumatoid arthritis, temporomandibular joint displacement with and without capsulitis, DeQuervain's disease and tendonitis. In these studies, iontophoretic dosage is ranged from 40 – 80 mA-min with treatments targeted at every other day for a total of six to eight dosing sessions. The evidence from these recent studies suggest that iontophoresis of dexamethasone sodium phosphate is superior to placebo. Patient benefits from receiving corticosteroids via iontophoresis include the reduction of pain, improved range of motion and the avoidance of adverse effects associated with systemic administration of higher doses of corticosteroids. In clinical practice, iontophoresis of dexamethasone and oral NSAIDs is routinely used for the treatment of inflammatory musculoskeletal disorders.

6.2 Local dermal anaesthesia

Medical care providers have long recognised the importance of pain management, including pain associated with certain minimally invasive medical procedures such as needle

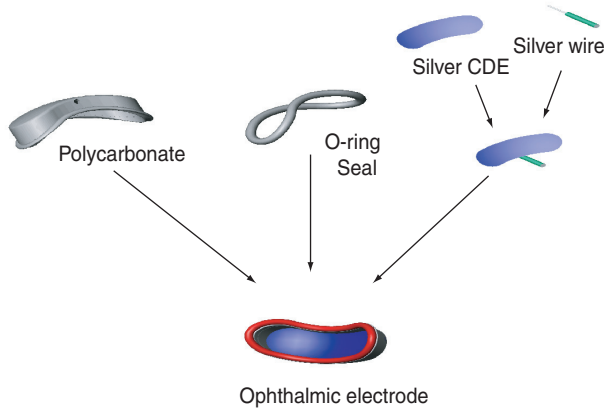

Figure 2. Opthalmic drug delivery system iontophoresis device. Schematic of transscleral iontophoretic delivery electrode courtesy of IOMED, Inc.
CDE: Current distribution element.

injections; venous access (including phlebotomies and intravenous catheterisations); lumbar punctures; local dermatological procedures such as wart and mole removal; biopsies (including fine needle, punch, excisional, shave and cervical biopsies); Mohs procedures and vasectomies.

Numby Stuff is used for the delivery of Iontocaine (lidocaine HCl 2% and epinephrine 1:100,000 topical solution). Numby Stuff offers noninvasive, needle-free local dermal anaesthesia in as little as 10 min and can be used prior to needle sticks, intravenous starts, lumbar punctures, peripherally inserted central catheter insertions, and fine needle and skin biopsies.

The delivery of lidocaine/epinephrine by iontophoresis for local skin anaesthesia has been studied in 12 published double-blinded, randomised, placebo-controlled trials involving > 357 subjects. The scientific evidence permits conclusion that when compared with placebo, iontophoresis effectively delivers lidocaine resulting in local skin anaesthesia prior to skin puncture for intravenous cannulation or blood draw [18,19,46]. Iontophoretic dosage averaged 40 mA-min in these studies. Double-blinded studies provided evidence that when compared with sham iontophoresis, iontophoresis of lidocaine achieved significant reductions in pain scores [20,21,47]. In double-blinded, placebo-controlled studies utilising ordinal pain scales, 62 – 100% of the subjects receiving lidocaine/epinephrine via iontophoresis reported no pain at anesthetised skin sites when tested by pinprick or during skin puncture procedures [19,23,48]. The adverse effects reported in these trials were similarly distributed in the treatment and placebo groups. These cutaneous, nonsystemic events were generally mild, transient and self-limiting. Additional databases on more than five million applications of the technology indicate that in current practice, dermal adverse effects involving burns rarely occur in association with iontophoresis with proper equipment. Thus, the available evidence indicates that the benefits of iontophoresis for the delivery of local anaesthetics may be obtained without significant short- or longterm adverse effects.

In three randomised, double-blinded comparative trials involving > 39 subjects [21,22,49], iontophoresis of lidocaine provided significantly better analgesia than a topical eutectic mixture of local anaesthetic (EMLA) prior to skin puncture ($p < 0.001$, $p < 0.05$, $p < 0.001$, respectively). The results of Squire *et al.* [50], in a randomised, non-blinded study of 100 paediatric patients, supported these findings. Although the absence of blinding in this latter study may represent a methodological flaw, the effects produced by iontophoretic lidocaine in the larger patient population of this study were consistently superior to EMLA and corroborated the observations of the smaller studies. The available data indicates that iontophoresis of lidocaine requires a shorter time to achieve effective local skin anaesthesia than EMLA (3 – 30 min versus 60 min, $p < 0.001$) [21,50]. The shorter time required to establish effectiveness makes iontophoresis particularly beneficial for paediatric patients undergoing painful skin puncture procedures or for other patients whose conditions require emergent treatment.

7. Ocular iontophoresis

The German scientist Wirtz documented the use of iontophoresis in ophthalmology as early as 1908 for the treatment of corneal ulcers, keratitis and episcleritis [51]. Early ocular iontophoresis devices designed for animal studies were inconvenient to use and not standardised. This made it difficult to achieve reproducible results and the devices were impractical for human use [52,53]. With these early devices, the eye tissue was often damaged due to the extremely high current densities (300 – 600 mA/cm^2) that were applied to the eye [54,55].

Modern iontophoretic devices specific for ophthalmic drug delivery have been developed and patented [301,305]. These devices are simple to use and designed for commercial manufacture; however, so far no device has received FDA approval for ocular delivery of a specific drug. One advanced ophthalmic drug delivery device developed by IOMED (**Figure 2**) is designed as a practical, single-use ophthalmic electrode that can be used in an ophthalmologist's office with minimal pretreatment procedure and minimal technique dependency. The drug delivery system incorporates a specialised drug containment hydrogel matrix fitted inside a reservoir or shell. This device uses a silver/silver chloride current distribution element (CDE) to control the hydrolysis of water and resultant pH changes that would otherwise occur during iontophoresis. 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. The device is placed in the lower cul-de-sac of the human eye and the eyelid holds the device in place during treatment (**Figure 3**). Current and dosage time can be programmed and controlled through the use of a sophisticated electronic current controller that delivers

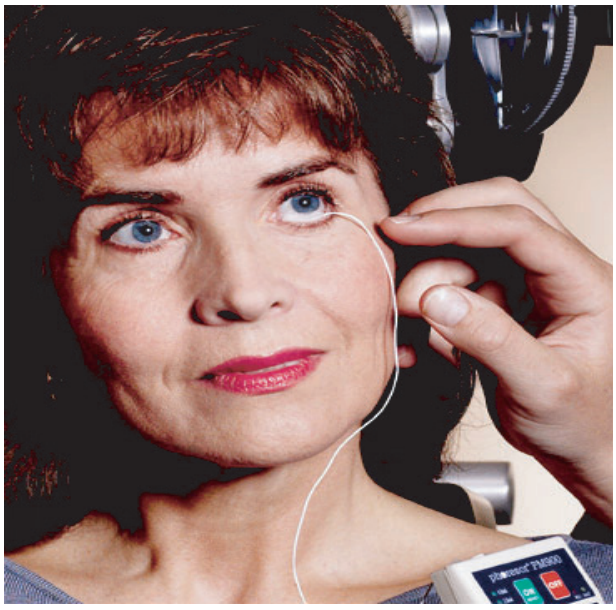

Figure 3. Placement of transscleral iontophoretic delivery electrode. Photograph courtesy of IOMED, Inc.

constant current and is designed to be placed conveniently away from the patient during a treatment session.

An area of significant potential in the field of ophthalmology and one of the most studied is the iontophoretic delivery of antimicrobial agents. Delivery of antibiotics in sufficient quantity to achieve microbiologically inhibitory levels into the eye to treat bacterial endophthalmitis and keratitis has been extensively evaluated. Researchers have tried subconjunctival, retrobulbar, intravenous and intramuscular injections of a variety of antimicrobials, but found most did not achieve adequate drug levels in the target tissue [56-60]. A number of *in vivo* experiments with rabbits have demonstrated greater drug delivery of a variety of antibiotics using iontophoresis. Streptomycin [57], tobramycin [61,62], amikacin [67] and gentamicin [64-66] have been delivered into the cornea, aqueous humor and retina/choroid.

Vollmer *et al.* [67] performed a distribution and reproducibility study using amikacin delivered via transscleral iontophoresis in rabbits. Amikacin is an aminoglycoside antibiotic used against ocular infections. The study showed concentrations of amikacin were highest in the sclera and retina/choroid after 20 min of iontophoresis at a current level of 4 mA. The levels of amikacin detected in the vitreous humor, anterior segment, sclera and retina/choroid were all well above the 0 mA control group and greater than the *in vitro* minimum inhibitory concentrations (MICs).

Dexamethasone sodium phosphate is currently used topically in the eye. Problems associated with topical corticosteroid use for the treatment of ocular disease include poor intraocular penetration into the posterior segment of the eye and secondary side effects when given systemically. A number of studies have been performed delivering the anti-inflammatory steroids dexamethasone sodium phosphate and methylprednisolone hemisuccinate via iontophoresis to the eye [68-71].

Szlek *et al.* [69] performed a single application pharmacokinetic study with ^{14}C radiolabelled dexamethasone sodium phosphate. The results of their study showed that >50% of the radiolabelled dexamethasone cleared from the target tissues (iris/ciliary body and retina/choroid) during a 1.5-h period 0.5 – 2 h after the initiation of the iontophoresis treatment. There were no differences in dexamethasone clearance (first order elimination kinetics) from any of the treated eye tissues. The researchers concluded that the tissue retention and half-life data were consistent with intravitreal and subconjunctival injections reported in the literature.

Fischer *et al.* [72] reported data showing intra- and interstudy reproducibility of delivering diclofenac (a NSAID) via transscleral iontophoresis in rabbits. Conclusions from the study were that drug delivery was significantly enhanced by iontophoresis and was more reproducible than the passive control (drug in contact with the sclera with 0 mA current). On average, transscleral iontophoresis yielded a 16-fold increase in diclofenac concentrations in the retina/choroid compared with a passive control group.

Table 3 lists numerous other compounds evaluated using ocular iontophoresis.

7.1 Safety of ocular iontophoresis

Parkinson *et al.* [73] published a human tolerance study where 24 healthy subjects were iontophoresed transclerally with a balanced salt solution. In this study 16 subjects received 0 mA and two of the following DC currents: 0.1, 0.5, 1, 2, 3 or 4 mA for 20 min; six subjects received 3 mA for 20 min and 1.5 mA for 40 min. Safety and tolerance to the electric current were determined by subjective VAS and objective assessments (slit lamp, visual acuity, funduscopy, Goldmann applanation tonometry, Ishihara colour vision test and fluorescein staining). The iontophoresis sessions were well tolerated and no clinically significant changes in ophthalmic assessments were noted after either the 0 – 3 mA for 20 min or 1.5 mA for 40-min treatments. Two of the four subjects treated at a 4 mA current level reported a burning sensation under the electrode. For these subjects, superficial changes in fluorescein staining were observed at 1 h; however, this resolved by 22 h postdose.

8. Summary and conclusions

Methods commonly used in clinical practice for drug delivery include topical administration, tablets, capsules, solutions/suspensions, aerosols, passive transdermal patches and injections. Topical and passive transdermal applications are noninvasive; however, drug diffusion through the stratum corneum is inefficient and highly dependent on molecular size and structure. Systemic delivery of drug to treat disease generally requires high levels of circulating drug to achieve therapeutic levels,

Table 3. Compounds evaluated with ocular iontophoresis.

Class	Compound	Ion	Application	Model	Ref.
Adrenergics	Timolol maleate	Cation	Penetration study	Rabbit	[106]
	6-Hydroxydopamine	Cation	Glaucoma	Human	[107]
Angiogenics	Carboplatin	Anion	Retinoblastoma	Rabbits	[108]
	Combretastatin	Anion	Proof of principle	Rabbits	[63]
Antibiotics	Amikacin	Cation	Reproducibility	Rabbits	[67]
	Cephazolin	Anion	Safety	Rabbits	[53]
	Ciprofloxacin	Cation	*Pseudomonas* spp.	Rabbits	[109]
	Gentamicin	Cation	*Pseudomonas* spp.	Rabbits	[64-66,109]
	Ticarcillin	Anion	Safety	Rabbits	[53]
	Tobramycin	Cation	*Pseudomonas* spp.	Rabbits	[61,62,109]
	Vancomycin	Cation	Safety	Rabbits	[110]
Antifungals	Ketoconazole	Cation	Safety	Rabbits	[111]
Anti-inflammatories	Dexamethasone	Anion	Therapeutic levels	Rabbits	[68-70]
	Methylprednisolone	Anion	Inflammation	Human	[70,112,113]
	Diclofenac	Anion	Reproducibility	Rabbits	[71]
Antivirals	Ara-AMP	Anion	HSV	Rabbits	[114]
	Foscarnet	Anion	Safety	Rabbits	[115,116]
	Ganciclovir	Anion	Cytomegalovirus	Rabbits	[117]
	Idoxuridine	Anion	Comparison	Rabbits	[118,119]
	Vidarabine	Anion	Herpes	Rabbit/human	[118,120]
Gene transfer	4.7 kb plasmid DNA	*	Proof of principle	Mice	[121]
	230 base pair DNA	*	Proof of principle	Human	[122]
Oligonucleotides	anti-VEGF	Anion	pK	Rat	[123,124]

*Charge is pH and sequence dependant.

HSV: Herpes simplex virus; pK: Pharmacokinetic; VEGF: Vascular endothelial growth factor.

increasing the potential for unwanted side effects when oral and intravenous routes of administration are used. In addition to injection methods, sustained-release and biodegradable implants are being used to achieve continual therapeutic levels of drug. However, all these methods are invasive and carry the risk of infection and systemic side effects.

Iontophoresis is noninvasive and can be site-specific. Iontophoresis minimises the possibility of trauma and the risk of infection that is present with injections and associated invasive drug-delivery modalities. Iontophoresis avoids the pain and anxiety caused by needle injections. Research using iontophoresis has shown delivery of a number of therapeutic drug classes including antiangiogenics, anti-inflammatories, antibiotics and antivirals. Specific drug delivery profiles can be programmed by controlling the electric current applied and a dosage regimen can be tailored to the specific indication and needs of the patient. Iontophoresis systems can be designed to deliver predetermined and well-controlled 'baseline' doses as well as patient-activated (on-demand) 'bolus' doses to relieve breakthrough pain. An example of an application very well suited for programmed control include a patient-controlled analgesia (PCA) system that administers an opioid analgesic such as fentanyl hydrochloride, in a manner similar to the already existing PCA pumps for pain management after postoperative surgery and for cancer patients [74].

9. Expert opinion

Increasing patient acceptance, minimising risks and delivering a therapeutic dose specifically to diseased tissue are formidable challenges. Advances in iontophoretic electrode design and methods to optimise iontophoretic drug delivery have improved the ability to safely deliver both older, off-patent drugs as well as new chemical entities being developed to treat a variety of diseases, including conditions that affect the back of the eye. Iontophoretic drug delivery has slowly been gaining acceptance as a mainstream alternative transdermal drug delivery method. Two companies (IOMED, Inc. and Vyteris) have transdermal drug/device systems with a NDA approved by the US FDA for local dermal anaesthesia [301,302]. Alza Corporation [303] received an approvable letter from the FDA in July 2004 for their systemic fentanyl HCL transdermal iontophoresis delivery system. With acceptance of iontophoresis as a commercially viable delivery system, research and commercial development should accelerate for drug delivery using iontophoresis.

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Patents

201. ALZA CORP.: US4744787, US4747819, US5135477, US5573503, US5711761.

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