Iontophoresis: A Novel Approach for Drug Delivery
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ABSTRACT
Transdermal delivery is a well-accepted route of drug administration that provides an alternative to traditional methods, including oral and injection. Iontophoresis is a noninvasive technology based on the principle that like charges repel one another. A typical iontophoretic device is worn on the skin and consists of two electrodes, one (the anode [+] in a reservoir containing the positively-charged drug in solution and the other (the cathode [−]) in a negatively-charged salt solution. A power controller applies a voltage to the electrodes, which creates a mild electrical current that repulses the positively charged drug from the anode into the bloodstream where it is rapidly absorbed and distributed systemically. Iontophoresis is a technique that facilitates movement of ions of soluble salts across a membrane under an externally applied potential difference that is induced across the skin by a low-voltage electric current. The application of constant current is controlled by an electronic device that adjusts the voltage in response to the changes in skin electrical resistance. Charged drugs as well as other ions are carried across the skin as a component of induced ion flow. Iontophoresis effectively delivers a large variety of compounds across the skin.

Keywords: Noninvasive, Electrodes, Electric current, Iontophoresis

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Received on: 20-10-2013
Accepted on: 01-11-2013
Published on: 25-11-2013
INTRODUCTION

Iontophoresis is a noninvasive drug delivery option that employs a direct electrical current to introduce ions of soluble salts or other drugs into the body. Iontophoresis technology is based on the principle that an electric potential will cause ions in solution to migrate according to their electrical charges. In practice, an ionic drug is propelled by an electric field across intact skin and into underlying tissue. Ions are transferred at a rate proportional to the magnitude of the current flow.\(^1,2\) In addition, the quantity and distribution of a drug delivered into and across the skin by iontophoresis is dependent on the charge and molecular weight of the ion, duration of current flow and other factors.

Iontophoresis has been used in a wide variety of biomedical fields viz. dermatology (palmar hyperhidrosis, male contraception, ulcers, allergy testing, cystic fibrosis, scleroderma), ophthalmology (delivery of atropine, scopolamine, gentamycin, fluorescein), ENT (providing anaesthesia of external ear canal in facial prosthetic surgeries), dentistry (local anaesthesia for multiple tooth extraction), neuropsychological (as a research tool for studying neuromuscular junction, peripheral and central nervous system), muscle skeletal disorders (Mg for bursitis, Ca for myopathy, Ag for osteomyelitis, local anaesthetics and steroids into elbow, shoulder and knee joints) and drug delivery like counterirritants, antihypertensives, antidiabetic, antirheumatoids, hormones, vasodialators etc. In iontophoresis, a small electric current forces molecules into the skin. An electrode patch containing the drug is placed on the skin and this acts as the working electrode. This can be either positive or negative, depending on the characteristics of the drug. Another electrode is placed elsewhere to complete the electrical circuit and a small current of 0.5 mA/cm\(^2\) is applied to deliver the drug through the skin. Iontophoresis thus uses an electrode of same polarity as the charge on the drug to drive ionic (charged) drugs into the body by electrostatic repulsion. In order to deliver a positively charged drug across the skin, a solution of, for example, a cationic drug is placed at the positive electrode where it is repelled and then attracted towards a negative electrode place elsewhere on the body. Delivery of positively charged compounds is generally easier than negatively charged compounds as the skin itself possesses a net negative charge.\(^3,7\)

Principle of Iontophoresis

Iontophoresis increases the penetration of electrically charged drugs into surface tissues by the application of an electric current. Electrical energy assists the movement of ions across the stratum corneum according to the basic electrical principle of "like charges repel each other and opposite charges attract". The drug is applied under an electrode of the same charge as the charge on drug, and a return electrode opposite in charge to the drug is placed at a neutral site on the body surface. The operator then selects a current below the level of the patient's pain threshold and allows it to flow for an appropriate length of time. The electrical current significantly increases the penetration of the drug into surface tissues by repulsion of like charges and attraction of opposite charges. The two classically considered prerequisites for iontophoretic treatments are that the drug must be charged (or modified to carry a charge) and that the disease process must be at or near a body surface. The two principle mechanisms by which iontophoresis enhance molecular transport across the skin are pure iontophoresis, in which a charged ion is repelled from an electrode of the same charge and pure electro-osmosis, the convective movement of solvent that occurs through a charged "pore" in response to the preferential passage of counter-ions when the electric field is applied. The phenomenon of electro-osmosis has been used as a means to augment the anodic delivery of (in particular) large, positively charged serum, the transport numbers of which are often extremely small (and whose iontophoretic enhancement therefore depends heavily upon electro-osmosis) and to promote the transdermal migration of uncharged, yet polar, molecules, the passive permeation of which is typically very small. The choice of drug is of importance depending on weather the compound is unionized or ionized. Non-ionised compounds are generally better absorbed through the skin than ionized substances. The penetration across the skin and other epithelial surfaces is usually slow due to their excellent barrier properties. Many drug candidates for local applications only exist in an ionized form, which makes effective membrane penetration possible.

Advantages of Iontophoresis

Iontophoresis has the advantages over conventional administration methods thus no systemic side effects. Precise pH regulation, allows delivery of the maximal dosage (80 mAmp/min). Highly absorbent drug reservoir
minimizes the occurrence of high density current pathways. Conformable and adherent adhesive layer minimizes leakage of drug being administered. Low electrical impedance reduces constrictions of the voltage gradient as current passes through the active electrode. Large return electrode area lowers sensation and increases comfort. Low profile, drug delivery electrode conforms to complex geometries of the wrist, elbow, knee, finger, and ankle. Precise anatomic positioning, saving clinician intervention time. Virtually painless when properly applied. Provides option for patients reluctant or unable to receive injections. Reduced risk of infection due to non-invasive nature. Medications delivered directly to the treatment site. Minimizes potential for tissue trauma from an injection. Treatments are completed in minutes. Bypasses the hepatic first pass effect and gastrointestinal vagaries. The drug is delivered into the bloodstream directly without any delay. It also provides a rapid termination of the effect by turning off the iontophoretic delivery system.

**Disadvantages of Iontophoresis**

Although iontophoresis drug delivery system has much to offer there are some disadvantages associated with this technology. The delivery system is much more complicated than other transdermal delivery systems because power supply devices and circuitry, electrodes and specific drugs ion transfer are involved. In addition electrochemical stability could be a serious problem for some drug candidates. The cost of developing and manufacturing iontophoresic drug delivery system is much higher in comparison with that of other transdermal systems. There is a possibility of burns if the electrodes are improperly used. The formation of undesirable vesicles and bullae in skin being treated can be avoided by periodically interrupting a unidirectional treatment current with a relatively short pulse of current in the opposite direction. Side effects such as erythema, skin irritation or minor burns were observed in iontophoreric applications in dermatology. Toxic effects are not clear when metal ions resulting from dissolution of the metallic electrodes get into the skin and tissues.

**Reverse Iontophoresis.**

Reverse iontophoresis, a technique in which low electric current is applied to draw intestinal fluid through the skin, is widely applied now a days in devices meant for diagnostic application. This provides a convenient and non-invasive method for sampling of body fluids so as to permit simultaneous measurement of the desired substance in the body fluid and thus to monitor them efficiently e.g., devices like Glucowatch uses the reverse iontophoresic process to continuously monitor the glucose level in the blood. This system provides a needless means of monitoring blood glucose levels in diabetic patients and uses an electrical signal that is proportional to the amount of glucose in the extracellular fluid. This technique not only provides non-invasive sampling but also provides filtered samples free from large molecules. Although this technique provides for less tedious sampling, for it to be successful, it needs a very sensitive analytical method since the amount extracted is very low.

**Recommendations for iontophoresis machine safety**

Ensure that users read the operators manual for the Iontophoresis machine, follow the operating procedures, and understand the associated hazards. Ensure good skin contact with the Iontophoresis machine electrode. Avoid placing electrodes on areas that have been recently shaved or over skin defects; broken skin and/or gaps between skin and electrode offer reduced resistance, thereby resulting in localized higher current concentrations. Advise the patient to report any sensation of pain or burning during treatment of the Iontophoresis machine. Adjust the current output to zero or minimum before the Iontophoresis machine is turned on or off. Do not turn the device on until the electrodes have been placed and the lead wires have been attached to the electrodes and to the device. Do not remove the Iontophoresis machine electrodes or disconnect the lead wires until the power has been turned off. If a problem occurs, remove the Iontophoresis machine from service and have it inspected.

**Applications of Iontophoresis**

**Sweat Chloride Test**

This test is used to help diagnose cystic fibrosis, an inherited disease of the exocrine glands that produces abnormal secretions leading to a build-up of mucus. This build-up of mucus can impair the pancreas, intestines and finally the lungs. If left untreated, cystic fibrosis leads to death in 95 percent of children before they reach the age of 5.

In the sweat chloride test, iontophoresis is used to administer the drug pilocarpine. It is a painless procedure applied to the forearm or back that induces sweating. An electrode is placed over a dose of pilocarpine and low
current is then applied. This causes the skin to sweat. The sweat is then absorbed into a special filter paper and the chloride content of the sweat is measured. Normal sweat chloride levels are between 10 to 35 milliEquivalents/liter. People with cystic fibrosis usually have sweat chloride levels greater than 60 milliEquivalents/liter. Intermediate levels of 35 to 60 milliEquivalents/liter can be seen in some cystic fibrosis patients and children. If intermediate levels are measured, it is recommended that the sweat chloride test be repeated in a month.

**Treatment for Hyperhidrosis**

Hyperhidrosis is a condition that causes the sweat glands on the palm of your hands, soles of your feet and your armpits to be overactive. Used since the 1950s, iontophoresis can not cure hyperhidrosis but it can help to alleviate some of the excessive sweating. While the exact way iontophoresis accomplishes this is not known, it is thought that the application of a low electrical current somehow plugs some of the sweat glands in the affected area and temporarily prevents them from sweating. The area to be treated is placed in a tub of water and electrodes pass a small electrical current through the water. It is most effective for the treatment of hands or feet. The technician administering therapy will increase the intensity of the current until the patient feels a mild tingling sensation. Sessions last from 10 to 20 minutes and many sessions are required for the desired results. Side effects are minimal and may include redness, skin cracking and blistering. Home iontophoresis devices are available.

**Treatment for Bursitis and Tendinitis**

Bursitis is caused by overuse or a direct injury to a bone or joint. A bursa is a small fluid-filled sack that acts as a cushion between a bone or other moving parts of the body. Tendinitis is normally caused by a repetitive injury in the affected areas. A tendon is the flexible band of fibrous tissue that connects a muscle to a bone. People suffering from gout, arthritis, diabetes and thyroid disease are more likely to develop tendinitis or bursitis. When iontophoresis is used in the treatment of bursitis and tendinitis, a low electrical charge is used to administer a corticosteroid medication through the skin directly over the bursa or tendon that is affected. This is done similarly to the sweat test by an electrode applied to the skin with a dose of medication. Massage and gentle strengthening exercises are added to the treatment to ease symptoms.

**Home Iontophoresis Devices**

No drugs are used in this therapy. Devices for use on the hands and feet consist of two suitcase-like tubs to hold water. Electrodes are placed inside the tubs and are connected to a power source. To administer iontophoresis, you place your hands or feet into the tubs of water and the current is turned on. Therapy sessions last from 10 to 20 minutes. The device used for treatment of the armpits consists of electrodes inside of a cloth that is dampened and held under the arms. The advantage of home iontophoresis therapy is the convenience. People who have irregular heartbeat, a pacemaker or any metallic implants at the treatment site are advised not to use home iontophoresis devices. Side effects are uncommon and may include skin irritation and blisters.

**Dermatologic Applications of Iontophoresis**

Iontophoresis has been used for the treatment of various dermatologic conditions. The majority of published studies are either uncontrolled series or anecdotal observations. Earlier, simple ions and heavy metals were the most frequently used drugs, but over the last 30 years interest has shifted toward the use of iontophoresis as a drug delivery system for a wide variety of medications, ranging from steroids to antibiotics to local anesthetics.

**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. complete healing was reported in four of the five patients. Cornwell reported a patient with ischemic ulcer who responded to iontophoresis with solution of zinc oxide.

**Fungal infection**

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

**Viral Infections**

Warts: There is a report of the successful treatment of plantar warts with sodium salicylate iontophoresis. Herpes simplex: Gangarosa reported that iontophoretic application of idoxuridine was effective in aborting episodes of herpes simplex. Lekas reported relief of discomfort and reduction of healing time of herpes simplex lesions in a controlled trial using iontophoresis with idoxuridine.

**Aphthous stomatitis**
In a small group of patients with aphthous stomatitis, iontophoresis of triamcinolone acetonide showed immediate relief of discomfort in the prodromal stage, but for lesions beyond the prodromal stage relief was not achieved until after 36 hours.

Lichen planus
In an uncontrolled series, Gangarosa reported iontophoresis with methyl prednisolone for erosive lichen planus, which healed with fibrosis.

Hyperhidrosis
The most successful application of iontophoresis is for the treatment of hyperhidrosis. The basis for such treatment and its practical aspects has been well described. Currently, the most commonly used conducting medium is tap water because it is safe and effective. Anticholinergic compounds (e.g. poldine methyl sulfate, glycopyrronium bromide, and atropine) have a longer lasting effect than water, but the side effects of systemic anticholinergic blockade have prevented their wide acceptance. The efficacy and safety of tap water iontophoresis is well documented, but its mechanism of action remains unknown. The most widely accepted hypothesis is that sweating is inhibited by mechanical blockage of the sweat ducts at the stratum corneum level, the depth and severity of the damage being dose-related. Stripping off the stratum corneum relieves the blockage and restores sweating. More recent work by Hill et al casts doubt on this theory. They examined, by light and electron microscopy, sweat glands from the palm of a patient with hyperhidrosis before and after treatment and found no changes.

Anesthesia
Otolaryngologists have used iontophoresis of local anesthetics for anesthesia of the middle ear, and dentists, for anesthesia of the oral mucosa. Anesthesia of the skin can be achieved with the use of a variety of positive and negative controls, including iontophoresis of epinephrine and lidocaine separately, and topical administration of lidocaine and epinephrine. Skin anesthesia is best obtained with solutions containing 1% and 4% lidocaine and between 1/10,000 and 1/50,000 epinephrine. Iontophoresis of anesthetics may be useful especially for pediatric patients.

Miscellaneous uses
Hyperkeratosis with fissuring of palms and soles: Iontophoresis with 5-10% aqueous solution of sodium salicylate showed improvement within a period of 3-4 weeks (6-8 sittings of 10-15 minutes each).

Vitiligo: In an uncontrolled study, iontophoresis with meladine solution 1% in patients with vitiligo showed marked repigmentation.

Scleroderma: In one trial, iontophoresis with hyaluronidase led to increased skin softness and flexibility of tissues and decreased cold sensitivity. On termination of therapy, cold sensitivity returned in a week but the improvement in skin softness and flexibility persisted for three months.

Lymphedema: Iontophoresis with hyaluronidase has also been successfully used in the treatment of lymphedema of the limbs.

Patch testing: Wahlberg reported encouraging results with the use of iontophoresis as a complement to ordinary patch testing in the investigation of obscure cases of contact eczema. With iontophoresis, the test substances are administered rapidly and they migrate through the epidermis down into the dermis. Additionally, the disadvantages of the traditional patch test procedure, such as prolonged wearing of the test strips, are eliminated.

Sweat test: Iontophoresis was also used for the diagnosis of cystic fibrosis by the sweat test. Iontophoresis with pilocarpine causes rapid sweating for minutes. Other applications of iontophoresis include introduction of "artificial skin pigment" (iron oxide and titanium oxide) into the skin, iodine iontophoresis to reduce scar tissue, and administration of antibiotics (penicillin) in burn patients.

Iontophoresis devices and Mechanism
A typical iontophoresis device consists of DC voltage delivery system and electrodes. Wires are then connected between the unit and the active and passive electrodes, and the unit set for current and time. In the iontophoresis process, the current, beginning at the device, is transferred from the electrode through the ionized drug solution as ionic flow. The drug ions are moved to the skin where the repulsion continues moving the drug through the transappendageal structures and stratum corneum interstices via the aqueous pores. The larger the electrode surface, the greater the current the device must supply to provide a current density for moving the drug. Iontophoresis enhances transdermal drug delivery by three mechanisms
(a) ion-electric field interaction provides an additional force that drives ions through the skin.

(b) the flow of electric current increases the permeability of the skin, and
(c) electro-osmosis produces bulk motion of solvent that carries ions or neutral species with the solvent stream.

Electro-osmotic flow occurs in a variety of membranes and is in the same direction as the flow of counter-ions. It may assist or hinder drug transport. Since human skin is negatively charged above pH 4, counter ions are positive ions and electro-osmotic flow occurs from anode to cathode. Thus, anodic delivery is assisted by electro-osmosis but cathodic delivery is retarded. Because of the electro-osmotic flow, transdermal delivery of a large anion (negatively charged protein) from the anode compartment is more effective than that from the cathode compartment. Iontophoretic devices may be powered by electricity, batteries or by rechargeable power sources. The machines available in India are electric operated. Battery operated units are Drion, Phoresor etc. A Phoreser device consists of a microprocessor-controlled battery powered DC current, drug reservoir and electrodes. The batteries are most commonly 9 volt ones. The drug reservoir consists of a gauze/cloth or gel pad to which the solution is applied or the solution is injected through a port into the reservoir electrode combination. Wires are connected between the microprocessor unit and the active and passive electrodes. Iomed iontophoretic drug delivery electrodes are available and are composed of hydrogel material that is hydrated before use to deliver local anesthesia. An external energy source in the form of an applied direct electrical current will increase the rate of penetration by assisting the movement of ions, driving the drug across the skin. Like charges repel each other and opposite charges attract. Thus, positive ions in a water-soluble medication are repelled from a positively charged electrode positioned over the tissue into which the medication ions are to be delivered, and negative drug ions are repelled from a negatively charged electrode. The direct current moves the ions from the drug electrode through the patient’s skin. During iontophoresis, a shift in pH occurs due to hydrolysis of water. The competing ions may result in a less efficient drug transfer. Buffers may be built into the electrode to minimize this effect, but the buffer materials should be bound or immobile so they do not compete with the active drug. Products that use chemical buffers added to the electrode reservoir are undesirable as these introduce a high concentration of extraneous mobile ions. The buffer ions then compete with the drug ions for current and reduce the overall delivery efficiency of the system.

Preparation of treatment site
The treatment site should be carefully prepared. The skin should be cleansed with alcohol. The treatment site should be free of trauma and excessive body hair. Shaving can cause micro abbreviation to the skin so clipping excess hair is recommended. Electrode placement is important and the electrodes should be applied carefully. The treatment electrode should be placed directly over the area to be treated if possible. The electrodes should be well adhered to the skin. Loose electrodes can contribute to thermal burns and skin irritation. The patient should not extend or flex the area being treated or press or lean against the electrodes during treatment. The electrodes should be secured; however, never bind or tape the electrodes to the treatment area. Electrodes should never be reused.

FDA Regulations
The objective of the Food and Drug Administration (FDA) is to assure that the device is equivalent to a predicate device and is as safe and effective as a predicate device on the market. The FDA clears iontophoresis medical devices via a 510(k), a process in which the manufacturer has to prove the safety and efficacy of their medical device to the predicate medical device by a series of tests and labeling. It restricts these devices to sale by or on the order of a physician. The FDA allows companies to market these devices as intended to be used for the administration of soluble salts into the body for medical purposes and as an alternative to hypodermic injection. The FDA will allow a specific drug to be mentioned if and only if it has been cleared via an NDA (New Drug Application).

Factors Affecting Iontophoretic Delivery
When selecting drug candidate for iontophoretic drug delivery one must consider factors that may influence the iontophoretic drug delivery properties.

The charge of drug ion
The drug molecule must be in an ionized state with either a positive or negative charge. The number of charges on the molecular ion has a direct potential effect on the rate of its migration in an electric field. Therefore a divalent molecular ion is expected to move faster than a monovalent ion through the same medium.
Current strength
Drug ion transport is a function of total current and the fluxes of other ions present. However, the rates of transport of other species are also dependent upon the total current.

Figure 1: Mechanism of Iontophoretic drug delivery

The conductivity of drug candidate
Conductivity of drug in aqueous solution is a good parameter for selecting drug candidate. The specific conductivity of drugs gives an estimate of ease of movement in solution when an electric current is applied. Suitable electric conductivity is an important factor in the successful transdermal transport of drugs by iontophoresis.

The pH of vehicle used in drug reservoirs
Most of the drug molecules are weak electrolytes and therefore poor passive precutaneous permeants. Under normal pHe conditions if the drug molecules can be kept in a reasonable highly ionized form they can be administered transdermally using iontophoretic techniques.

The competition of extraneous ions in the drug reservoir
The presence of buffer species or salt ions in the drug reservoir has negative effect on iontophoretic drug delivery of drug molecule owing to their competition with charged drug molecules for the applied electric current. However, the presence of any drug counterions carrying the opposite charge does not have any adverse effect on the iontophoretic delivery of charged drug molecules.

The Pka of drug candidate
Most iontophoretic experiments both in vivo and in vitro are carried out at a pH of about 5. The pH of the skin has been reported to be 5. Therefore, it is wise to choose drug candidate that has a Pka value that will maximize the amount of drug existing in ionized form.

Aqueous solubility of drug candidate
The aqueous solubility of drug candidate dictates the amount of drug that can be dissolved into the reservoir. Most drug candidates are in salt salt form so solubility is not usually a problem unless the drug is lipophilic.

Molecular weight of drug candidate
The larger the drug molecule, higher the resisting force and slower the migration of the ion through the medium. The potential of skin irritation and sensitization. The transport of number of drug candidates:-

Effect of temperature
Increase in temperature increases mobility of ions. Electrochemical study of drug candidate:-

Electroosmotic effect
Electro osmotic flow is defined as the volume flux of liquid through a membrane caused by an electric field imposed across the membrane. The imposed electric stimulus causes a net force on unpaired ions that exist in a very thin region near the liquid-solid interface within the system of the membrane; this region is called the electrochemical double layer and results from the absorption of ions to the surface of solid.

Biological factors
These factors involve the skin to which the electrodes are applied; its thickness, permeability, presence of pores, etc. Sweat glands are the most significant path for the conduction of charges into the skin.

CONCLUSION
Iontophoresis has been explored for many dermatologic and other medical conditions with reports of considerable success. In this drug delivery drug is targeted at the particular site hence greater absorption and bioavailability. Very less amount of drug reaches to other body organs hence no chances of other toxic side effects. Iontophoretic drug delivery has greater permeability of drug and hence it is best way for treatment. Iontophoresis is gaining wide popularity as it provides a non invasive and convenient means of systemic administration of drugs with poor bioavailability profile, short half life and with multiple dosing schedules. Iontophoresis, in comparison to oral route, definitely provides benefits of improved efficacy and/or reduction in adverse effects.

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Conflict of Interest: None declared