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Review Article

Iontophoresis: Principle and Its Applications

Dr. B. V. Ramana*, Yakkanti Anjani, Shaik Farooq, Bandi Likhitha

Dr. K. V. Subba Reddy Institute of Pharmacy, Dupadu, Kurnool.

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ABSTRACT

Iontophoresis is a fascinating technique that utilizes a low electric current to facilitate the transdermal delivery of ions and charged molecules. This method has garnered significant interest in recent years as an alternative to traditional drug delivery systems, especially for targeting localized conditions and minimizing systemic side effects. This review provides an in depth examination of the principles underlying iontophoresis, including its mechanisms, equipment, and factors affecting drug transport. Key applications in dermatology, pain management and treatment of hyperhidrosis are highlighted, showcasing the therapeutic potential of iontophoresis across diverse medical fields. Additionally, we address recent advancements, such as the development of novel drug formulations and enhanced device technologies, which have improved the efficacy and broadened the applications of iontophoretic drug delivery. Challenges, including skin irritation and variability in individual responses, are discussed alongside potential strategies for overcoming these limitations. This article aims to present a comprehensive overview of iontophoresis and its growing role in modern medicine, while also identifying future research directions for optimizing its clinical use..

INTRODUCTION

Transdermal medication delivery is becoming more and more significant in contemporary pharmacological therapy. When non-ionized medications are needed in modest dosages, it is utilised. It is possible to administer transdermally passively or with assistance. The non-ionized medication enters the skin through the stratum corneum during passive delivery. Due to its semi-permeable nature, the skin only permits a minimal quantity of medication molecules to infiltrate the skin [1]. Ionised medications are difficult to pass through this barrier, hence routine transdermal distribution is not recommended unless an outside energy source is available to push the medication through the skin. Facilitated diffusion is assisted by electrical energy through iontophoresis, electroosmosis and convective water flow [2]. Iontophoresis, also called ionophoresis, electrophoresis or cataphoresis is a technique for

***Corresponding Author:** Dr. B. V. Ramana
Address: Dr. K. V. Subba Reddy Institute of Pharmacy, Dupadu, Kurnool.
Email ✉: anjaniyakkanti80808@gmail.com

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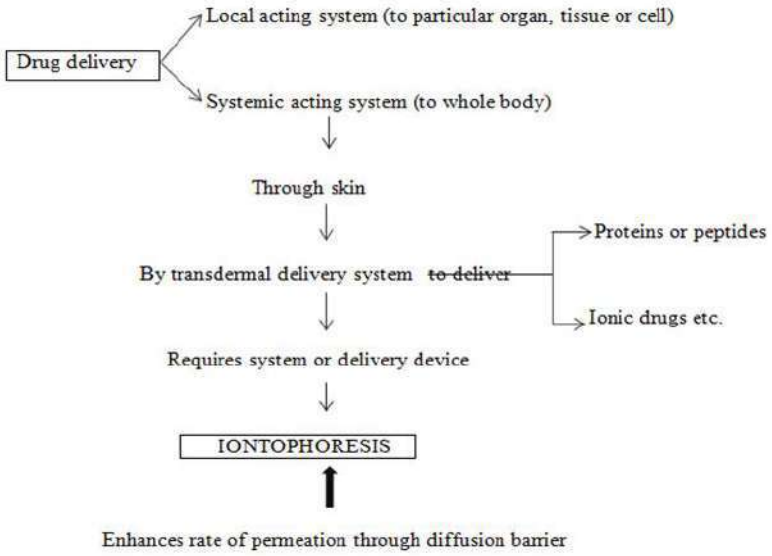
increasing the therapeutic absorption of ionic medications into the body by applying an electrical current [3]. Iontophoresis works by making opposite charges attract and like charges repel, which significantly enhances ion penetration. Positive lidocaine ions, for instance, are drawn to the cathode and repelled from the anode. Comparably, negative iodothuridine ions are drawn to the anode and repelled from the cathode [4].



The following are the features of iontophoresis process for local therapy:

1. The drug used should be charged (ionic);
2. It should be applied at the electrode of the same charge;
3. The disease or condition being treated must be at or close to a body surface and
4. Therapy is improved because the drug is concentrated in the tissue of application [6].

Many medications with low penetration qualities such as high molecular weight electrolytes like proteins, peptides, and oligonucleotides, which are often difficult to supply other than the parenteral route, have utilized in this method's potential for transdermal administration. Iontophoresis has demonstrated a significant penetration of bigger peptides such as insulin for which there have been a number of iontophoretic studies with hardly any report demonstrating that iontophoresis can even reach human insulin's baseline levels in vivo [7].

Historical Background of Iontophoretic Process:

The term "iontophoresis," which comes from the Greek words "ionto," which means "ion," and "phoresis," which means "to bear," refers to a technique that uses a small amount of electricity to enhance the number of ionized molecules that can enter or flow through tissue. The use of electricity in clinical settings dates back to the Greek civilization's golden age and was most likely by Varatti in 1747 [8]. Important contributions were made by the French physician Bernard Raymond Fabre Palaprat (1773-1833) [9]. Using his own arm, Samuel George Morton (1799-1851) performed an experiment in which he applied electric current after connecting graphite powder to a positively charged electrode [10]. Benjamin Ward Richardson, acknowledged as the "father of dental iontophoresis" (1828–1896), found the "voltaic narcotism," a method for oral anaesthetic delivery. In the 1870s, the German Hermann Munk (1839-1912) performed experiments with primitive equipment laid the ground work for the subsequent discoveries of proteins and processes of active transport in biological membranes in the 20th

century. The mid-18th century saw the first suggestion for the use of electric current in medicine administration. In the 19th century, significant advancements were made, most notably by William James Morton (1846–1920). During the time of Stephen Leduc (1853–1939) and Fritz Frankenhausener (1868), attempts were made to administer metal ions in addition to alkaloids. Before 1908, Frankenhausener is credited with coining the word "iontophoresis" [11]. Today, the treatment of hyperhidrosis is the most successful and popular applications of iontophoresis in dermatological medication (Sloan JB et al., 1986). The first commercial devices are available in the market (Kalia et al., 2004) [12]. Behar-Cohen et al. assessed the use of iontophoresis in rats receiving parenteral delivery of dexamethasone in combination with ocular application of the medication [13]. On rabbit corneas, gentamicin sulfate and iontophoresis were evaluated by Frucht-Pery et al [14]. In place of analyzing endogenous chemicals to diagnose renal failure, Wascotte et al. employed reverse iontophoresis, which collects material via the skin, and correlated this with blood sample [15].

Basic Principles of Iontophoresis:

Basic principles:

Iontophoresis is a fascinating procedure that facilitates the transfer of charged and uncharged molecules over the skin by means of a small, specified electric current. Three fundamental components make up an iontophoretic system:

1. An energy source of electronic current, which usually consists of a battery and controlled electronics;
2. An active reservoir, which contains the ionic therapeutic agent; and
3. An indifferent or return reservoir system, which contains an electrolyte and serves to complete the electric circuit
4. Also a control system, to monitor the overall process [16].

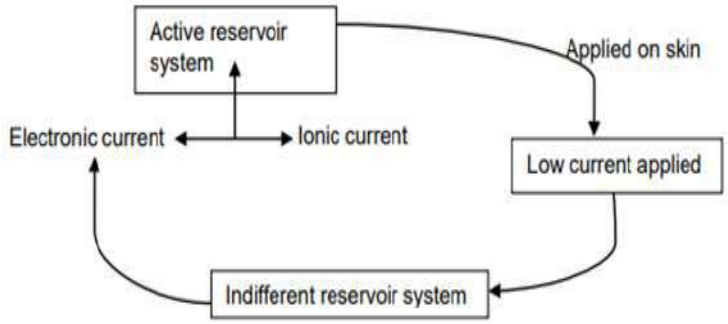


Figure 1. Schematic representation of iontophoretic process

The reservoirs may only contain saline or buffer when using reverse iontophoresis for clinical monitoring. The current source drives electronic current to the active reservoir, where it is converted into ionic current, when the active and indifferent reservoir systems are applied to the skin. Ionic current travels via the active reservoir, the skin, the indifferent reservoir underneath the skin, and back through the skin into the indifferent reservoir. It is converted back into electronic current at the indifferent reservoir, finishing the circuit at the current source's opposite pole. An electrode with a defined charge repels a substance that is attracted to an oppositely charged electrode that is positioned elsewhere on the body. Therefore, a positively charged medication or ion in solution, an electronic device to control the current, an anode reservoir system (with the anode electrode), and a cathode reservoir system (with the cathode electrode) make up an anodal

iontophoretic device. The cathode is applied to a different area of the skin than the positively charged medication, which is placed in the anode reservoir system at the intended application site. All cations, including the positively charged medication, migrate into the skin and away from the anode when an electric current is applied. In parallel, the body's negatively charged ions flow from the body into the donor reservoir [17]. An anodal iontophoretic system is shown in Fig 2.

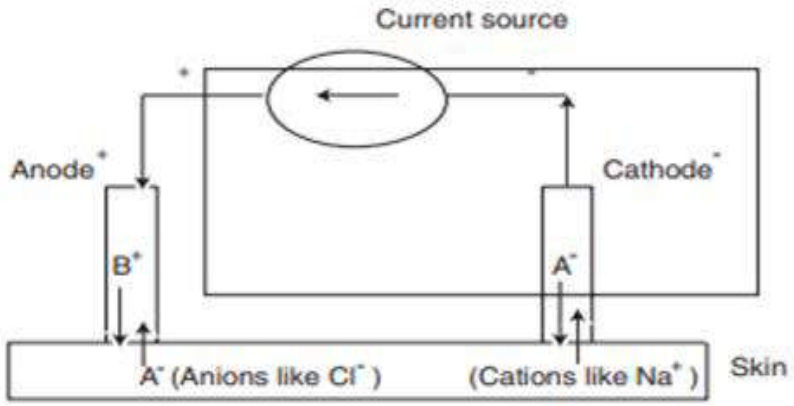


Figure 2. An anodal iontophoretic process

Electrode system in iontophoresis:

The form and shape of the electrodes that are selected should conform nicely to the skin's surface and cause the least amount of pH changes in the skin. Silver/Silver chloride (Ag/AgCl) electrodes have been commonly used in iontophoretic systems. The silver present at the anode oxidizes and reacts with chloride ions to form insoluble AgCl. As of right now, the AgCl at the cathode gets reduced to Ag^+ and releases the Cl^- .The reactions do not involve the electrolysis of water [18].

Types of electrodes:

- Traditional electrodes
- Commercial electrodes

Electrodes have a small chamber covered by a semipermeable membrane into which ionised solution may be injected [19].

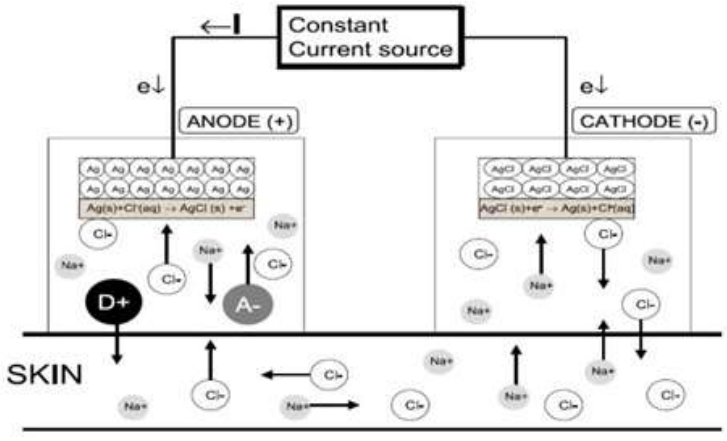


Figure 3. Iontophoresis and Drug Delivery

Transport Mechanisms:

Abramson and Gorin derived an equation to compare the iontophoresis flux due to electric

mobility, electroosmosis and simple diffusion. The increased flux during iontophoresis would include:

- Flux due to the electrochemical potential gradient across the skin;
- Change in the skin permeability due to the electric field applied; and
- Electro-osmotic water flow and the resultant solvent drag.

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

$J_{electric}$ –The flux due to electric current application;

$J_{passive}$ – The flux due to passive delivery through the skin; and

$J_{convective}$ - The flux due to convective transport due to electro osmosis. The total flux of a solute (J_I) across the skin during iontophoresis is the sum of electro-migration (J_{EM}), electro-osmotic (J_{EO}), and passive diffusion (J_P) contributions [20].

$J_I = J_{EM} + J_{EO} + J_P$

According to Faraday's law, the electro-migration flux of each ion in the iontophoretic circuit at steady state is given by

$$J_{EM=}\frac{t_i * I}{F * Z_i}$$

Where, t_i is the transport number, and z_i is the valence of ith ion, F the Faraday's constant and I is the total current. The transport number depends on the ion's relative mobility (μ_i) and charge, and upon its concentration (c_i) relative to those of the other ions present:

$$t_i = \frac{c_i * z_i * u_i}{\sum_{i=1}^{n}(c_j * z_j * u_j)}$$

Since the saline is the primary extracellular electrolyte that the body contains in large quantities, Na^+ and Cl^- ions always carry the majority of the current during in vivo iontophoresis. High molecular weight cations and uncharged compounds are mostly transported by electroosmosis. Because of its negative charge at physiological pH, the skin functions as a cation-selective membrane [21]. Neutral molecules are carried in the anode to cathode direction by an electro osmotic solvent flow caused by the preferred passage of counterions. The potential gradient created by the electric field is proportional to the volume flow v (volume * time −1 * area −1).

$$v = L_{ve} * -\frac{d\emptyset}{dx}$$

Where L_{ve} is the electro-osmotic flow coefficient describing the direction and the magnitude of the volume flow induced by the driving force, $-\frac{d\emptyset}{dx}$.The electro-osmotic flux contribution to the transport of a solute "j" present in the anodal compartment at a molar concentration c_j is then [22].

$$J_{EO} = v * c_j$$

At pH 7, electroosmosis slows the transit of anions while facilitating the transport of high molecular weight cations. It can be changed by adjusting the membrane's permselectivity and adjusting the formulation in the electrode chambers. For small ions such as Na^+ or Cl^-, electromigration dominates; on the other hand, neutral solutes are transported only by electro-osmosis and passive diffusion [23]

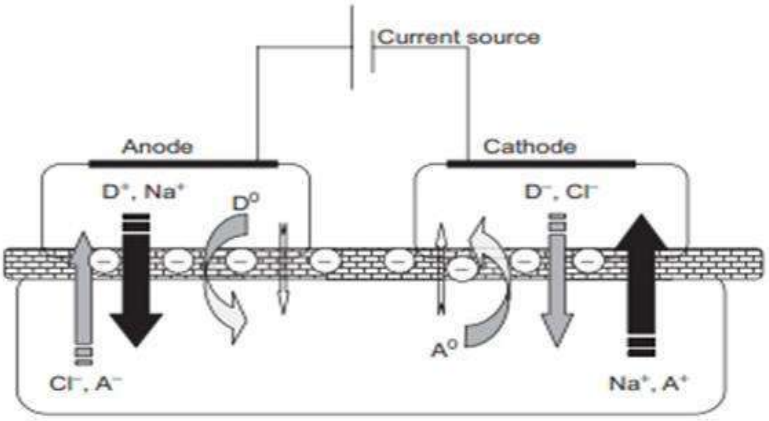


Figure 4.Transport mechanisms of iontophoresis

Pathways Of Molecular Transport In Iontophoresis:

The application of current can also create changes in the permeability and create new pathways for drug permeation. Although there are three routes for a drug to permeate through the skin:

- Intercellular (paracellular) between the corneocytes;
- Intracellular (transcelular) through cells;
- Appendageal (shunt pathway) hair follicles sweat ducts, secretary glands [24]

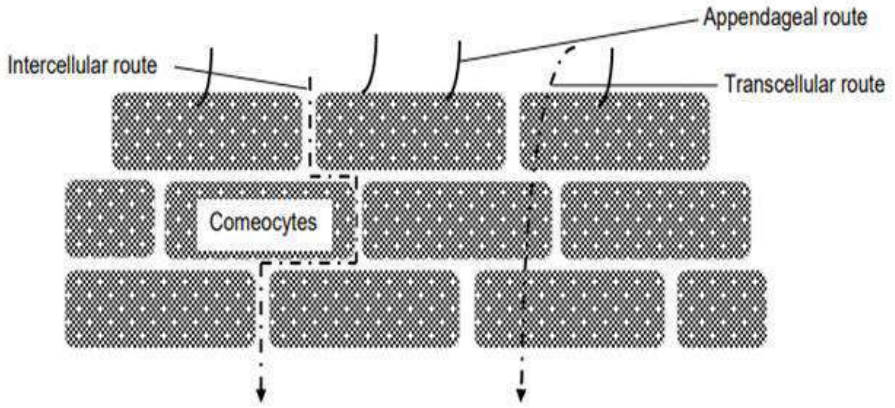


Figure 5. Pathways of Molecular Transport in iontophoresis

Types Of Iontophoretic System:

The system of drug delivery via iontophoresis can be classified in accordance to the modification and improvement done in this system which allows the uniform and predictive drug release in an effective manner. The types are:

- Reverse iontophoresis
- Pulsative/ switching iontophoresis
- Iontophoresis and electroporation combination [25]

Factors Affecting Iontophoretic Delivery System:

❖ **Operational factors:**

➢ **Drug formulation:**

- Concentration of drug
- pH of donor solution
- Ionic strength
- Presence of co-ions

➢ **Physicochemical properties of the drug candidate**

- Molecular size
- Charge
- Polarity
- Molecular weight
- Salt form of a drug

➢ **Experimental conditions:**

- Current density
- Current strength
- Pulsed current
- Duration of application
- Electrode material
- Polarity of electrode
- Current continuous vs. pulsed mode

❖ **Biological factors:**

- Intra and inter subject variability
- Regional blood flow
- Skin pH
- Condition of skin
- Patient anatomical factors [26]

ADVANTAGES:

1. It is a non-invasive technique could serve as a substitute for chemical enhancers.
2. It eliminates problems like toxicity, adverse reactions associated with presence of chemical enhancers.
3. It may permit lower quantities of drug as compared to use in TDDS.
4. TDDS of many ionized drugs at therapeutic level was precluded by their slow rate of diffusion under a concentration gradient, but iontophoresis enhanced flux of ionic drugs across the skin under electrical potential gradient.
5. Eliminate the chance of over dosing or under dosing by the continuous delivery of drug programmed at the required therapeutic rate.
6. It is important in systemic delivery of peptide / protein based drugs, which are very potent, extremely short acting and often require delivery in a circadian pattern to stimulate physiological rhythm Examples: Thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, interferons, enkaphaline etc.
7. Provide simplified therapeutic regimen, leading to better compliance.
8. Permit a rapid termination of the modification, if needed, simply by stopping drug input from iontophoretic delivery system.
9. Provide predictable and extended duration of action.
10. Reduce frequency of dosage.
11. Self-administration is possible.

DISADVANTAGES:

1. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.
2. An excessive current density results in pain.
3. Burns are caused by electrolyte changes within the tissues.
4. Minor reactions such as erythema, itching and general irritation of the iontophoretic skin surface.
5. The safe current density varies with the size of electrodes.
6. The high current density and time of application would generate extreme pH, resulting in a chemical burn.
7. This change in pH may cause the sweat duct plugging perhaps precipitate protein in the duct, themselves or cosmetically hyper-hydrate the tissue surrounding the ducts.
8. Electric shocks may cause by high current density at the skin surface.
9. Possibility of cardiac arrest due to excessive current passing through heart.
10. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.
11. High molecular weight 8000-12000 results in a very uncertain rate of delivery [27].

Applications:

- It is used to study the efficacy of iontophoretic delivery of calcium for treating hydrofluoric acid induced burns.
- It is applicable in the treatment of hyperhidrosis. Hyperhidrosis is a condition which results in excessive sweating in the hands and feet.

- Iontophoresis method is used to diagnose the cystic fibrosis based on the electrolyte composition that is affected by the disease [28].
- Iontophoresis of antibiotics has been shown to be more effective for treating superficial infections [29].
- This method has also been used for the treatment of allergic rhinitis by using zinc [30].
- It is a preferred method for obtaining anesthesia for the tympanic membrane.
- It has been used to deliver the antibiotics into the eye [31].
- Electro-osmotic flow generated by application of low level current has been used for the extraction of glucose through skin [32].
- The delivery of vasopressin, oligopeptides is done with the help of transdermal ionto-therapeutic system [33].
- It is used to deliver Hyaluronidase to scleroderma [34].
- Two potent vasodilators, histamine and mecholyl have been administered by iontophoresis for a variety of disorders [35].
- Copper iontophoresis has been used to treat chronic fungal infections of the feet. Magnesium sulphate is used in the treatment of sub-deltoid bursitis [36].
- Iontophoresis with dextran free 0.1% riboflavin-5-phosphate solution is used in keratoconus.
- Hypersensitivity reactions can be reduced by application if 2% NaF or HEMA-G iontophoresis [37].

Table 1: Drugs used in iontophoresis treatment

S. No	Name of the drug	Class of the drug	Trade name	Use/ Indication
1.	Lignocaine along with epinephrine	Local anaesthetic	Akten, Lignospan forte, Oraqix, Zingo	To reduce pain
2.	Dexamethasone phosphate	Steroid	Dalalone, Dexasone, Dexacen, Dexamethasone solurex	For the treatment of uveitis and other inflammatory eye conditions
3.	Fentanyl HCl	Opioid	Ionsys	Ensures patient controlled analgesia in acute and moderate to severe postoperative pain
4.	Ketoprofen	Non-steroidal anti-inflammatory drugs (NSAIDs)	Orudis, Orudis KT, Oruvail, Alrhumat and Kefenid	Increased drug retention in skin and has potential in topical therapy of musculoskeletal diseases
5.	Celecoxib	NSAIDs	Celebrex	Used to treat osteoarthritis, acute pain, joint inflammation and joint injuries

6.	Ciprofloxacin	Fluoroquinolones	Ciloxan, Ciproxin, Cetraxal, Cipro, Proquin	Delivery into the aqueous humour for the treatment of intraocular infections
7.	Terbinafine	Anti-fungal agent	Lamisil and Terbinex	Provides fungicidal activity against dermatophytes, moulds and dimorphic fungi
8.	Acyclovir	Anti-viral agent	Zovirax	Used in the treatment of herpes simplex and Varicella zoster virus infections
9.	Cisplatin	Anti- cancer agent	Cisplatinum, Platamin, Neoplatin, Cismaplat	Used to treat skin basal cell and squamous cell carcinoma

Various Synergistic Approaches with Iontophoresis:

1. Iontophoresis in conjunction with electroporation
2. Iontophoresis in conjunction with chemical enhancers
3. Iontophoresis in conjunction with sonophoresis
4. Iontophoresis in conjunction with microneedles
5. Iontophoresis in conjunction with ion-exchange material [38]

Patents For Iontophoresis:

India has seen a range of patents filled for iontophoresis applications, particularly in therapeutic and medical contexts.

Table 2: Patents for iontophoresis

Title	United states patent	Issued	Inventors	Assignee	Application number	Filed
Iontophoretic electrode device, method and gel insert	4,383,529	May 17, 1983	Henry L. Webster, Providence, Utah	Wescor, Inc.,Logan, Utah	202,889	Nov 3, 1980
Wireless iontophoresis pad and controller	0266005	August 25 ,2022	Anton Sabiev, Forest Hills, NY (US), William Bauman, New Rochelle NY (US), Mark Korsten, Hastings- on-Hudson NY (US)	William Bauman	17/36,602	May 4, 2022

Iontophoretic delivery device with integrating hydrating means	6,223,075	April 24, 2001	Jon E.Beck, Lindsay B. Lloyd, Tomasz J. Petelenz	Iomed, Inc.,	08/762,051	Dec 9, 1996
Device and method for corneal delivery of riboflavin by iontophoresis for the treatment of keratoconus	9,700,456 B2	Jul.11,2017	Fulvio Foschini, Pierre Roy, Edoardo Stagni, Giovanni Cavallo, Giulio Luciani	Sooft Italia spa	13/824,850	Jan.12, 2011
Stabilized interface for iontophoresis	5,837,281	Nov 17, 1998	Katsumi Iga, Masafumi Misaki Keiichiro Okabe, Emi Kyo	Takeda chemicals industries, Ltd., Advance Co., Ltd., Teikoku Hormone Mfg. Co., Ltd.,	614,375	March 12, 1996
Iontophoresis patch equipped with donor gel and reference gel	20120310143A1	June 12, 2012	Yaegashi, Mitsutoshi, Hasui, Akihiro, Kubo, Hiroyuki	Yaegashi, Mitsutoshi	13/578,168	Feb. 09, 2012

CONCLUSION:

Iontophoresis is a word which is derived from the Greek “ionto” represents “ions” and “phoresis” represents “to bear”. Iontophoresis refers to a non-invasive technique that uses a small amount of electricity to enhance the number of ionized molecules that can enter or flow through tissue. It is a technique which represents for delivering drugs through the skin, offering a range of clinical applications from treating hyperhidrosis to enhancing the delivery of analgesics and anti-inflammatory agents. This method is utilized to deliver the high molecular weight substances like peptides, oligonucleotides etc. Its advantages include controlled, localized drug administration and reduced systemic side effects compared to traditional methods. It also by passes the first pass metabolism and gastric tract effects. It also offers patients compliance. However challenges such as skin irritation, variability in patient response, and limitations in drug types suitable for iontophoretic delivery remain areas for further research. Further advancements in electrode design, drug formulations, and personalized protocols could improve efficacy, safety, and patient outcomes, potentially broadening the utility of iontophoresis

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