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IONTOPHORESIS: A NEWER TECHNOLOGY

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ABSTRACT

Iontophoresis is an exciting technology that was initially investigated 250 years ago. Simply defined, it is the application of an electrical potential that maintains a constant electric current across the skin. Recently, there has been increased interest in using this technique for the transdermal delivery of medications, both ionic and non-ionic. In the past few years, different types of iontophoresis such as transdermal, ophthalmic, buccal and Ural iontophoresis have been reported. This article is an overview of the history, types and factors affecting iontophoretic drug transfer, external preparation, advantages, disadvantages, applications of iontophoresis.

KEYWORDS

Iontophoretic delivery, Factors, External preparation and Applications.

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INTRODUCTION¹

Iontophoresis is a technique using a small electric charge to deliver a medicine or other chemical through the skin. It is basically an injection without the needle. The technical description of this process is a non-invasive method of propelling high concentrations of a charged substance, normally a medication or bioactive agent, transdermally by repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged active agent

and its vehicle. One or two chambers are filled with a solution containing an active ingredient and its solvent, also called the vehicle. The positively charged chamber, called the anode, will repel a positively charged chemical, whereas the negatively charged chamber, called the cathode, will repel a negatively charged chemical into the skin.

Iontophoresis is well classified for use in transdermal drug delivery. Unlike transdermal patches, this method relies on active transportation within an electric field. In the presence of an electric field, electromigration and electroosmosis are the dominant forces in mass transport. These movements are measured in units of chemical flux, commonly $\mu\text{mol}/\text{cm}^2\text{h}$.

In order to deliver an ionic drug, peptide/protein molecule through transdermal delivery to attain a systemic effect, chemical and/or physical methods are required to enhance the rate of penetration of therapeutic agent through the main diffusion barrier. The iontophoretic technique is highly desirable to improve the transdermal delivery of peptide and proteins using a lower current intensity with a short time period. The idea of applying electric current to increase the penetration of electrically charged drugs into surface tissues was probably organized by Veratti in 1947.

When the membrane under consideration is skin, the method is called transdermal iontophoresis. The principle barrier to the transport of the molecules across the skin is stratum corneum (SC), i.e., the uppermost layer of the epidermis with a thickness of between 10-100 μm . The SC consists of several layers² of corneocytes (a nucleate keratin filled cells) inlaid in a lipid matrix, a continuous medium through the SC, arranged mainly in bilayers. The intercellular lipids consist of approximately equal quantities of ceramides, cholesterol and free fatty acids.

In iontophoresis, cationic or neutral therapeutic agents are placed under an anode or anionic therapeutic agents under a cathode. When a low voltage and low current density is applied,

according to simple electrorepulsion, ions are repelled into and through the skin. Cationic drugs are driven into and through the skin by the anode (active electrode), which also extracts anion from the tissue underneath the skin into the anode. At the cathode (return electrode) anionic buffer ions are driven into the skin and cations from the tissues are extracted into the cathode. It is also possible to include an additional charged drug in the return electrode to be delivered simultaneously or to use a mixture of drugs in the active electrode to enhance the desired effect or to increase skin permeation, depending on which drugs/molecules are used.

Percutaneous absorption³ may take place simultaneously by any combination of the three main pathways that include; the intercellular (paracellular) pathway between the connocytes along the lamellar lipids, the intracellular (transcellular) pathway through the cells or the appendageal (shunt) pathway via hair follicles, sweat ducts and secretory glands.

Ions prefer the routes of the least electrical resistance; in the SC this is believed to be via the pores. Some investigations indicate that these pores are sweat glands, others that transport occurs through both hair follicle and sweat glands.

The physicochemical properties of the molecules have an effect on the contribution of the follicular and non-follicular routes of penetration. Hydrophilic molecules tend to localize in the hair follicles, whereas lipophilic molecules are mostly distributed in the lipid intercellular regions of the SC and the lipid membranes of the epidermal keratinocytes. Since passive transdermal permeation of the majority of the drugs needs enhancement to achieve clinically relevant plasma concentrations, both chemical and physical enhancement methods have been developed.

TYPES OF IONTOPHORESIS

1. Anodal iontophoresis.
2. Cathodal iontophoresis.

Iontophoresis is usually defined as either anodal (+) in which the positive anode is placed in the solution applied to the epidermis and negative cathode is placed in the dermal receptor solution, or cathodal (-), in which the electrode location are reserved. Anodal (+) inotophoresis is facilitated by the movement of a cation from the donor to the receptor, whereas cathodal iontophoresis implies the movement of an anion from the donor to receptor.

History of Transdermal Delivery System⁴

The first proposal for the use of electric current in the drug delivery dates from the mid 18th century. Serious progress was made in the 19th century notably by Benjamin Ward Richardson (1828-1896). Hermann Munk (1839-1912), William James Morton (1846-1920), Stephen Leduc (1853-1939) and Fritz Frankenhauser (born 1868). Administration of metal ions as well as alkaloids was tried at that time. Until the early 20th century, current medicated drug delivery was known as “cataphoresis”. Frankenhauser is said to have introduced the term “iontophoresis” before 1908. Recently researchers talk about “electrically-assisted transdermal drug delivery”. The technique was never widely adopted but always proved useful to some extent in solving particular drug delivery problems.

Twenty two years ago, the first transdermal drug delivery system was introduced in the US making a historic breakthrough, holding the promise that new compounds could be delivered in a safe, convenient way through this skin. And yet, during the last two decades, the commercial success of transdermal delivery has been slow to develop. But, as a spate of newer products and technologies move towards the market place, transdermal drug delivery seems to have arrived.

America's first commercially marketed transdermal patch used a passive mode of drug delivery that permitted the drug to diffuse through the avascular dermis to the deep dermis, allowing local action or penetration to the capillaries for a systemic effect. But these passive systems had limitations. This

approach depended on the drug's properties to facilitate transport through the skin by using a simple concentration gradient as a driving force. Also, few drugs were available with the right physicochemical properties to make good candidates for transport through the skin. Even with these limitations, passive transdermal patches are experienced ever-increasing acceptance today.

Factors Affecting Iontophoresis Transport⁵

Many factors have been shown to affect the results of iontophoresis. These include the physicochemical properties of the compound (molecular size, charge, concentration), drug formulation (types of vehicle, buffer, pH, viscosity, presence of other ions), equipment used (available current range, constant vs. pulsed current, type of electrode), biological variations (skin site, regional blood flow, age, sex), skin temperature and duration of iontophoresis. The following factors have to be considered:

Influence of pH

The pH is of importance for the iontophoretic delivery of drugs. The optimum is a compound that exists predominantly in an ionized form. When the pH decreased, the concentration of hydrogen ion increases and a vascular reaction (vasodilatation) is initiated because of C-fiber activation, thus it is important to keep the pH as close as possible to and, at least when working with vasodilators, at pH 5.5 and below. There is an increasing risk for vascular reaction due to the high concentration of hydrogen ions rather than the compound used. Since hydronium ions are small they penetrate the skin more easily than larger drug ions. Laboratory findings vary on the effect of pH and drug behavior. According to the Henderson-Hasselbalch equation, pH is the determining factor governing the amount of drug present in the ionized state. For optimum IP, it is desired to have a relatively large proportion of the drug in the ionized state. However, this must be counterbalanced with delivery of a drug at a pH that is tolerable and safe for the patient.

Current strength

There is a linear relation between the observed fluxes of a 1cm^2 , the current is limited to 1 mA due to patient comfort considerations. This current should not be applied for more than 3 min because of local skin irritation and burns. With increasing current, the risk of non-specific vascular reactions (vasodilatation) increases. At a current of 0.4-0.5 mA/cm² such a vascular reaction is initiated after a few seconds of iontophoresis with deionised or tap water. This latter effect is probably due to current density being high enough a small area to stimulate the sensory nerve endings, causing reactions such as the release of substance P from C-fiber terminals.

Current density

Current density is the quantity of current delivered per unit surface area. The following criteria should be considered in selecting proper current densities for IP. The current should be sufficiently high to provide a desired drug delivery rate. It should not produce harmful effects to the skin. There should be a quantitative relationship between the applied current. The drug should be electrochemically stable.

Ionic competition

In a solution of sodium chloride, there is an equal quantity of negative (Cl^-) and positive (Na^+) ions. Migration of a sodium ion requires that an ion of the opposite charge is in close vicinity. The latter ion of opposite charge is referred as a counter-ion. An ion of equal charge but of different type is referred as a co-ion. When using iontophoresis, it is important to know that pH adjustment is performed by adding buffering agents. The use of buffering agents as co-ions, which are usually smaller and more mobile than the ion to be delivered results in a reduction of the number of drug ions to be delivered through the tissue barrier by the applied current. In our example, this means that when a positively charged drug is diluted in saline, the sodium ions will compete with the amount of drug ions to be delivered. Ideally, the use of a buffer system should be avoided in iontophoresis, but if this is not possible, alternative

buffers, consisting of ions with low mobility or conductivity are preferred.

Drug concentration

Depending on the drug used, the steady-state flux (ion movement) has been shown to increase with increasing concentration of the solute in the donor compartment, i.e. in the delivery electrode. Increased uptake by the skin during and after IP with an increase in drug concentration has been reported⁶. A limiting factor to be considered is the strength of the current used. At higher drug concentration, probably because of the saturation of the boundary layer relative to the donor bulk solution.

Molecular size

It has been shown that the permeability coefficients in positively charged, negatively charged and uncharged solutes across human skin are a function of molecular size. When the molecular size increases, the permeability coefficient decreases. However, there are certain solutes with a relatively high molecular size (e.g. insulin, vasopressin and several growth hormones), which have also been to penetrate the skin barrier into the systemic circulation⁷.

Connective or electro-osmotic transport

When performing iontophoresis with a specific current, the flow of ions across the membrane induces a flow of solvent called electro-osmosis. Compared to the ion transport, the electro-osmotic contribution is small. The penetration of uncharged substances (e.g. bovine serum albumin) has been shown to be facilitated by the volume flow effect induced by an applied potential difference across the membrane. Iontophoresis has also been observed to enhance the penetration of a number of dipolar ions (zwitter ionic substances like phenylalanine). Most of these substances have been shown to be delivered in significantly higher amounts by anodic delivery than by cathodic delivery. In general, iontophoresis is more effective for charged compounds, especially monovalent ions.

Current-continuous vs. Pulsed mode

Application of a continuous current over a long period of time can modulate iontophoresis delivery. Continuous DC current may result in skin polarization, which can reduce the efficiency of iontophoretic delivery in proportion to the length of current application. This polarization can be overcome by using pulsed DC, a direct current that is delivered periodically. During the 'off time' the skin becomes depolarization using pulsed DC can, however, decrease the efficiency of pulsed transport if the frequency is too high. Enhanced iontophoretic transport has been reported for peptides and proteins by using pulsed Dc compared to convenient DC. Most of the drug ions used for diagnostic purposes in combination with iontophoresis and LDPM are small in size. As a result, the time needed for an effect is relatively short (5-20 s) compared to when iontophoresis is used for therapeutic purposes (20-40 min).

Physical factors⁸

Iontophoresis reduces intra and inter-subject variability in the delivery rate. This is an inherent disadvantage with the passive absorption technique. Experiments *in vivo* iontophoretic give support for clinical findings that there are small differences in the flux rate following transdermal iontophoresis between males and females, as well as between hairy and hairless skin. The status of the vascular bed is also important; for instance, a pre-constricted vascular bed decreases the flux through the skin while a dilated vascular bed increases the yield of the drug through the skin.

Drug salt form

Different salt forms have different specific conductivities and that conductivity experiments *in vitro* will provide information concerning the general suitability of a drug for IP. The salt form of drugs must be considered along with the pH of the solution for determining the amount of drug in the ionized state.

Patient anatomical factors

Patient anatomical factors that influence the depth of penetration that is variable from patient to patient include skin thickness at the site of the application, presence of subcutaneous adipose tissue and the size of other structures, including skeletal muscle. Additionally, the presence and severity of inflammation can influence drug penetration due to the increased temperature (which may increase and may serve to transport the drug throughout the body).

Type of matrix containing the drug, gel vs solutions

The migration of the drug under the influence of the electrical current will be different as the matrices are different. This can be related to differences in viscosities, material electrical charge and porosities.

Stability of the drug during the IP process

The drug undergoing IP must be stable in the solution environment up to the time of Ip and also during the iontophoresis process. Oxidation or reduction of a drug not only decreases the total drug available but the degradation compounds, if they possess the same charge as the drug ion, will compete with the drug ion and reduce the overall trans membrane rate of the drug.

Physico-chemical parameters

Physico-chemical parameters The movement of drug ions across the skin is dependent not only the magnitude of apparent electric field, but also upon the concentration of solution, the molecular size of drug to be passed, as well as charge and valence of ion.

pH

The iontophoretic drug delivery rate is dependent on the ionic form of drug delivery, which is extremely effected by the pH of the system, when the skin is maintained at a negative charge by exposing the solution with pH 4 or higher, it facilitate the transdermal delivery of cationic drugs.

Species variation

The wide differences in physical characteristics such as appendages per unit area, thickness and structural changes between human and laboratory rodent display a variation in penetration of drugs. The average penetration of drugs is in order of rabbit > rat > guinea pig > human. Human skin is very much less permeable than other rodents but iontophoretic delivery of drug is 7-fold greater in human skin consists of greater negative charge/or greater area fraction of negative pores.

Characteristics of Penetrants

The rate of penetration of substances through the intact skin depends on the size, charge, and configuration of molecules and relative solubility of the compound in lipid, water, in the Horney layer and on the vehicle in which the compound is presented to the skin. The iontophoresis gives uncertain drug delivery rate for an ionic solute of molecular weight 8000 to 12,000. For a negatively charged species; the size dependent flux enhancement neutralizes the influence of electric field. Conversely, positive charged species becomes increasingly important to affect the electric field as the size of permeant increases.

Concentration

The concentration dependent iontophoretic delivery has not been fully investigated, some of the authors reported that as the concentration of drugs viz. hydromorphones and acetate ions increase in reservoir system then permeation of drug also increases. The iontopheric delivery of insulin does not effected by the reservoir concentration at the current range of 0.2-0.8 MA. O'malley and Oester showed the flux of solute was non-linearly proportional to its concentration.

Buffer Systems

Buffer systems also affect the permeation of drugs by iontophoresis. It is important to optimize the concentration of buffer species in the system and should be sufficiently high to maintain good buffer capacity but should not reach an extent such that the current is mostly carried by the buffer species

instead of drug special which may result the low efficiency of iontophoretic permeation.

Ionic Strength

The ionic strength of a drug delivery system is directly related to the iontophoretic permeation of drugs. Some authors reported that increasingly the ionic strength of the system decreases the permeation rate of drug and has no significant effect on penetration up to the 0.5 V.

Temperature

The penetration of drug through skin is affected by dual effect of both humidity and temperature. The iontophoretic delivery follows the Arhenious equation and enhances drug permeation with temperature.

Electrical parameters

Current

The extent of charged molecules, which may penetrate through the skin, are theoretically proportional to the intensity of current and the duration of treatment for a transdermal iontophoretic delivery.

Voltage

The ionic flux due to an applied voltage drop across a membrane is based on the fundamental thermodynamic properties of the system. The diffusion of drug during iontophoresis follows Nernst-Planck equation. It states that the flux of the ionic drug due to applied electric field is directly proportional to the voltage drop and the charge of the ion.

Resistance

The electrical resistance of the skin varies widely with iontophoretic drug delivery. The resistance of the skin during iontophoretic application was much lower on sweat pores, especially when they discharge sweat. A slight fall in resistance occurs when electrode was interested in to the epidermis.

Frequency/Impedance

The variability of frequency dependent impedance of human skin ranges from 10 KHz to 100 KHz. The impedance of the skin decreases at higher

frequencies less time is available to accumulate the charge on the skin surface during an applied pulse.

Wave Form

The waveform also affects the iontophoretic delivery of drug. The insulin delivery was highest at sinusoidal waveform than square and triangular waveform.

Efficiency of drug delivery

Efficiency of drug delivery the efficiency of iontophoretic drug delivery can be defined as that fraction of all ions which cross the skin for each mole of electrons flowing through the external circuit. This can be calculated from the slope of the plot of drug delivery rate \otimes versus current (I), which flows the given equation: $R = R_0 + F_i \cdot I$ where, R_0 is the positive drug delivery using iontophoresis, F_i is the iontophoretic constant defined as the amount of drug (on a weight basis) delivered per unit-time per unit current.

Ideal characteristics of drugs

Physicochemical properties

- a. The drug should have a molecular weight less than approximately 1000daltons.
- b. The drug should have affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics are not conducive to successful drug delivery via the skin.
- c. The drug should have a low melting point.

Biological properties

- a. The drug should be potent with a daily dose of the order of few mg/day.
- b. The half-life of drugs should be short.
- c. The drug must not include a cutaneous irritant or allergic response.
- d. Drugs in the GIT are inactivated by hepatic first pass metabolism effects are suitable candidates for transdermal delivery.

Components

1. Power source for generating controlled direct current.
2. Electrodes that contain and disperse the drug.

3. Negatively or positively charged aqueous medication of relatively small molecule size (<8000 Daltons).

4. Localized treatment site.

External preparation⁹

1. An external preparation, comprising:
A hydrophilic polymer matrix agent; and an ion-exchange resin dispersed in the hydrophilic polymer matrix agent.
2. The hydrophilic polymer matrix agent comprises at least one of polyvinyl alcohol, collagen, chitosan, sodium alginate, hydroxy propyl methyl cellulose, carmellose etc.
3. The ion-exchange resin is obtained by introducing one of a cation exchange group and an anion exchange group into a polymer having a three-dimensional network structure.
4. The cation exchange group comprises one of a sulfonic acid group, a carboxylic acid group, and a phosphonic acid group.
5. The anion exchange group comprises one of primary to tertiary amino groups, a quaternary ammonium group, a pyridyl group, an imidazole group and a quaternary imidazolium group.

A method of applying an external preparation, comprising:

Supplying a hydrophilic polymer having an ion exchange function in a reservoir; spraying the hydrophilic polymer from a coating nozzle onto a biological interface; and applying a voltage between an inductor electrode in contact with the spray of the hydrophilic polymer and the coating nozzle. An iontophoresis device, comprising a working electrode structure comprising:

First electrode

A drug holding part for holding a drug solution containing drug ions of a first polarity, the drug holding part receiving power from the first electrode, wherein the drug ions are administered by applying an electrical potential of the first polarity to the first electrode in a state where the drug holding part is brought into contact with a coating film formed on a biological interface, the coating

film being composed of an external preparation containing: a hydrophilic polymer matrix agent; and an ion-exchange resin dispersed in the hydrophilic polymer matrix agent, the ion-exchange resin being introduced with an ion exchange group whose counter ion is of the first polarity, or an external preparation containing a hydrophilic polymer having a function of exchanging an ion of the first polarity.

Second electrode

An electrolyte solution holding part for holding an electrolyte solution, the electrolyte solution holding part receiving power supply from the second electrode, wherein the drug ions are administered by applying an electrical potential of the second polarity to the second electrode in a state where the electrolyte solution holding part is brought into contact with a coating film formed on a biological interface, the coating film being composed of an external preparation containing: a hydrophilic polymer matrix agent; and an ion-exchange resin dispersed in the hydrophilic polymer matrix agent, the ion-exchange resin being introduced with an ion exchange group whose counter ion is of the second polarity, or a hydrophilic polymer having a function of exchanging an ion of the second polarity.

Advantages of Iontophoresis¹⁰

1. It is a non-invasive technique could serve as a substitute for chemical enhancers.
2. It eliminates problems like toxicity problem, adverse reaction formulation problems associated with presence of chemical enhancers in pharmaceuticals.
3. Increases therapeutic efficacy by bypassing hepatic "first-pass" elimination-the reduction in the amount of the drug entering the systemic circulation, due to metabolism by the liver as the drug passes through the hepatic circulation after absorption from the gastrointestinal tract.

4. It may permit lower quantities of drug compared to use in TDDS, this may lead to fewer side effects.
5. Iontophoresis prevent variation in the absorption of TDDS.
6. Eliminate the chance of over or under dosing by continuous delivery of drug programmed at the required therapeutic rate.
7. Provide simplified therapeutic regimen, leading to better compliance.
8. Permit a rapid termination of the modification, if needed, by simply by stopping drug input from the iontophoretic delivery system.
9. It is important in systemic delivery of peptide/protein based pharmaceuticals, which are very potent, extremely short acting and often require delivery in a circadian pattern to simulate physiological rhythm, ex; Thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, interferons, etc.

Disadvantages of iontophoresis¹¹⁻¹²

1. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.
2. An excessive current density usually results in pain.
3. Burns are caused by electrolyte changes within the tissues.
4. The safe current density varies with the size of electrodes.
5. The high current density and time of application would generate extreme pH, resulting in a chemical burn.
6. This change in pH may cause the sweat duct plugging perhaps precipitate protein in the ducts, themselves or cosmetically hyper hydrate the tissue surrounding the ducts.
7. Electric shocks may cause by high current density at the skin surface.

CLINICAL APPLICATIONS¹³

Anaesthetics delivery¹⁴

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

Pain management¹⁵

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

Glucose monitoring and insulin delivery¹⁶⁻¹⁷

Electro-osmotic flow generated by application of low level current has been used for extraction of glucose through the skin. As the direction of glucose flow is in the opposite direction (in outward direction in skin) to conventional iontophoresis, it is called reverse iontophoresis. This property, in combination with *in situ* glucose sensors, has been used in Gluco Watch Biographer (Cygnus Inc., Redwood City, CA, USA). This device allows noninvasive extraction of glucose across the skin, allowing a diabetic's glycemia to be evaluated every 10 min over several hours. Initial clinical trials using iontophoresis of soluble insulin were unsuccessful. Transdermal delivery of insulin by iontophoresis has been accomplished in laboratory animals. In a study of diabetic rats, iontophoretic delivery of bovine insulin affected glucose levels. By contrast, iontophoretic delivery of a monomeric human insulin analogue produced a significant fall in plasma glucose in the rats.

Skin cancer

The treatment of skin cancers by radiotherapy is usually associated with many complications. Iontophoresis could be a solution for such complications. Chang et al 88 investigated the iontophoresis of cisplatin in the therapy of basal and squamous cell carcinomas in the skin and concluded that small lesions would respond best by iontophoresis. Vinblastine subcutaneous administration leads to necrosis and phlebitis, hence not recommended. Also, intralesional administration causes pain and reduces patient compliance.

Antiemetic drug delivery

Iontophoresis study using hairless rat skin to improve the domperidone delivery. A total of 6 hour iontophoresis resulted in 15 fold improvement in drug delivery.

Antiviral agents

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

Cardiovascular agents

Various studies have been conducted on cardiovascular drugs including antihypertensive drugs (calcium channel blockers and adreno-receptor blockers). The iontophoretic delivery of metoprolol using rabbit model has been investigated. Arterial pressure was induced by intravenous administration of methoxamine hydrochloride at the rate of $30 \text{ mg kg}^{-1} \text{ min}^{-1}$ for 2 hours. High frequency pulsed iontophoresis (50kHz, 30% duty cycle) at a current density of 0.08 mA cm^{-2} was begun 15 min after onset of the IV infusion. The metoprolol iontophoresis significantly

decreased the systolic blood pressure from 126 ± 9 to 86 ± 1 mmHg and diastolic pressure from 99 ± 7 to 72 ± 10 mmHg.

Dermatologic applications

Treatment of hyperhydrosis the most successful application of iontophoresis is for the treatment of hyperhydrosis. The bases for such treatment and its practical aspects have been well described. The efficacy of iontophoretic delivery of calcium for treating hydrofluoric acid-induced burns.

Ischemic leg ulcers Iontophoresis has been used for the treatment of patients with ischemic leg ulcers¹⁸.

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

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

Treatment of pigmentation disorders Vitamin C is known to both inhibit melanin formation and reduce oxidized melanin. However, vitamin C does not easily penetrate the skin. Iontophoresis treatment using an active form of vitamin C (namely magnesium ascorbyl phosphate or MAP) at 3.6% for 12 weeks resulted in significant reduction of pigmentation.

Treatment of post-acne scars using iontophoresis with 0.025% tretinoin gel. At the end of treatment,

in 94% of patients a significant decrease in the scar depth was observed clinically. In conclusion, tretinoin iontophoresis was found to be effective, noninvasive treatment of atrophic acne scars without causing disturbing side effects.

Peyronie's disease treatment In the practice of urology, the primary use for iontophoresis has been for the treatment of Peyronie's disease (PD). PD is characterized by the clinical symptoms of diseases is initial penile pain followed by development of Plaque, penile deviation, plaque calcification, penile deformation and erectile dysfunction. The majority of patients initially prefer conservative treatment. Indication for conservative therapy seems to be the early painful and progressive stage of the disease. The surgical correction is the treatment of choice for major penile angulation and deformation, a variety of medical regimens have been used to resolve pain, plaques and minor deviation. Oral vitamin E, potassium para aminobenzoate and tamoxifen, and intralesional injection of steroids, orgotein, collagenase, verapamil and interferon- α have shown differing grades of efficacy to reduce the symptoms of PD. However, except for Vitamin E, they have considerable side effects, such as gastrointestinal symptoms, this often leads to premature termination of para-aminobenzoate therapy. Local injections are extremely painful and require local anesthesia. Iontophoretic therapy for PD has been tried in three patients. The treatment consisted of three, 20 mints sessions weekly for two weeks with 1% cortisone cream applied directly over the penile plaque. A positive electrode was placed above the application site of cortisone cream and a negative electrode was placed at a neutral site (eg. thighs, abdominal wall). A current of 3 ± 5 mA was applied, depending upon the patient's tolerance. These three patients were successfully treated with iontophoresis in spite of having mature PD. It was demonstrated that a substance, such as verapamil, could be detected in PD plaques.

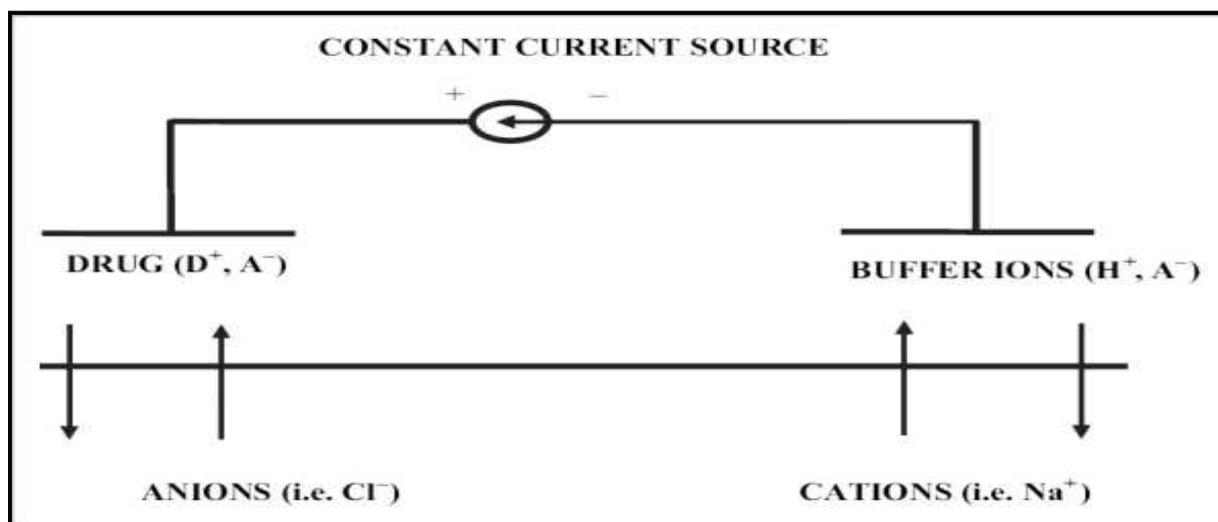


Figure No.1: Constant Current Source

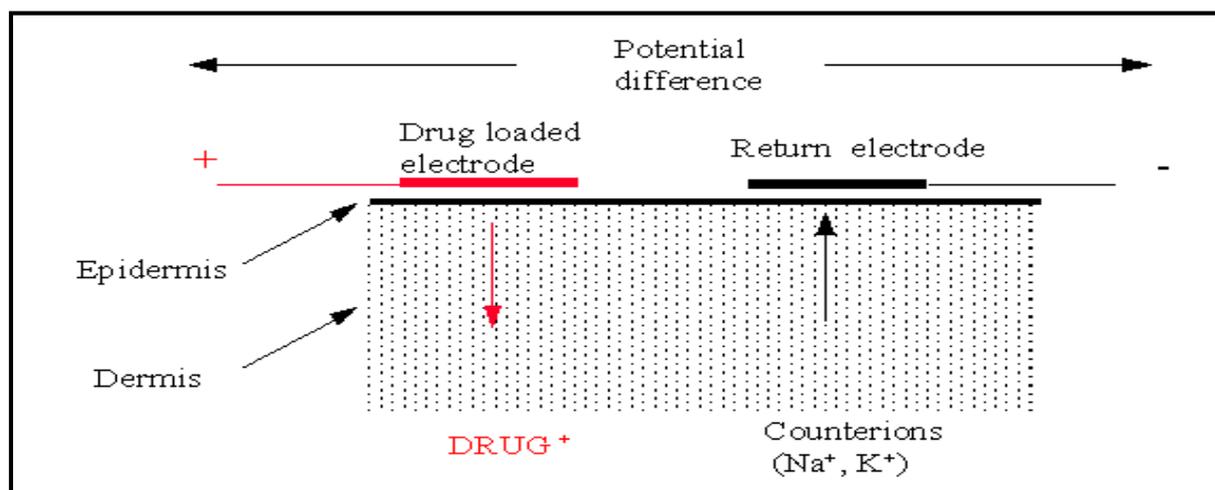


Figure No.2: Iontophoretic delivery of a positively charged drug through the skin

CONCLUSION

Iontophoretic system seems to be a potential alternative delivery system for charged species. Iontophoretic drug delivery has developed a new application system for dermal and transdermal delivery of drugs that is electrophoretically self-regulated device with electronic indicator. The controlled or feedback iontophoretic drug delivery may include the use of polymeric system. The iontophoretic delivery of macromolecules will open the doors to non-invasive transdermal delivery of peptide-based pharmaceuticals, following the

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advances in recombinant DNA technology, which are the wonder drugs of tomorrow.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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