



PHYSICAL PENETRATION ENHANCEMENT BY IONTOPHORESIS: A REVIEW

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ABSTRACT

The delivery of drugs into systemic circulation via skin has generated lot of interest during last decade. Iontophoresis is one of the physical approach in enhancement of transdermal permeation. This utilizes electric current as a driving force for permeation of ionic and nonionic medications. The basic principle of Iontophoresis is like charges repels each other and opposite charges attracts. Transdermal iontophoretic drug delivery provides constant blood level, avoids first pass metabolism, increased patient compliance and dose dumping never occurs. The protein, peptides and other macromolecules drug entities emerging from biotechnology research have provided their own special challenges in terms of delivery technology. However, the advancement in enhancement techniques like Iontophoresis which reversibly alter the barrier properties of skin can improve the penetration of such drugs. Iontophoresis seems to be an ideal candidate to sort out the limitations associated with the delivery of ionic drugs. In this review, efforts have been made to summarize all the aspects of iontophoretic delivery including history, types, various factors affecting the drug delivery and applications.

Keywords: Transdermal, iontophoresis, electrorepulsion; electroosmosis.

INTRODUCTION

There has been a growing awareness in recent years of potential therapeutic importance for achieving true controlled drug delivery, where the rate of drug output may be modulated in a precisely controlled manner. For several decades, there has been interest in using the skin as a port of entry into the body for the systemic delivery of therapeutic agents. Skin consists of membrane barriers, which are mainly composed of lipids & proteins. The penetration across epithelial borders is a slow process due to the effect of the barrier properties. The skin, in particular the stratum corneum, possesses a barrier to drug penetration due to its high density (1.4 g/cm² in dry state), its low hydration of 15 to 20 %. The barrier function is further facilitated by the continuous replacement of stratum corneum, there by limiting the topical & transdermal bioavailability.

Transdermal administration is used for non-ionized drugs required in a small quantity. Transdermal administration can be passive or facilitated, in passive administration; the non-ionized drug passes the skin through the stratum corneum. The skin, being a semi-permeable membrane, allows only a small quantity of any drug molecule to passively infiltrate the skin.¹

Iontophoresis can be defined as the process in which the flux or rate of absorption of ionic solutes into or through skin is enhanced by applying a voltage drop/electric field across the skin. Transdermal iontophoretic technique is capable of administering drugs in a pulsatile pattern by alternately applying and terminating the current input at programmed rate. In addition, delivery rate can be controlled by the intensity of applied electric current or electro-chemical potential gradient.

History

Iontophoresis, derived from the Greek "ionto" meaning ion and "phoresis" to bear, is a process that allows

increased penetration of ionized molecule across or in to the tissue by application of low electric current. Clinical application of current can be traced back to the ancient time of the Golden Age of the Greek Civilization. The idea of applying electric current to enhance the penetration of electrically charged drugs into surface tissue was probably originated by Varatti in 1747. In the later part of 19th century, Morton (1988) carries out an experiment to introduce graphite iontophoretically into his arm. The first well documented experiments were done at the beginning of 20th century by Leduc (1908). He demonstrated that rabbits suffered fatal seizures minutes after transcutaneous iontophoretic administration of strychnine.² Gibson and Cooke who studied iontophoresis technique in 1959 demonstrated an induction of sweating by iontophoretic application of pibocarpine.³ Further studies analyzed the use of iontophoresis for transporting steroids in the treatment of musculoskeletal e.g. rheumatoid arthritis, osteoarthritis and urological conditions e.g. Peyronie's disease.^{4,5}

Iontophoresis

Iontophoresis is a non invasive method of boosting high concentration of a charged substance, generally medication or bioactive agents, transdermally by repulsive electromotive force using a small electrical current applied to an iontophoretic chamber containing a similar charged active agent & its vehicle. The positively charged chamber, termed as anode will repel a positive charged chemical, while the negatively charged chamber, termed as cathode, which repel a negatively charged chemical into the skin. 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 $\mu\text{mol}/\text{cm}^2\text{h}$.

Abramson & Gorin derived an equation to compare the iontophoresis flux to electric mobility, electro osmosis &

simple diffusion.⁶ Other authors used a customized form of Nernst-Planck flux equation to explain the mechanisms of ion transport during iontophoresis application.^{7,8} The increased penetration of an ionic compounds achieved by applying an electric current can thus be due to the electrochemical potential gradient across the skin, increased skin permeability under the electric field, and a current-induced water transport effect (electro osmosis or convective transport).^{9,10}

$$J^{sp} = J^p + J^e + J^c$$

J^p is the flux due to passive delivery and is defined by:

$$J^p = K_s D_s dC / ds$$

K_s - partition coefficient between donor solution and stratum corneum, D_s - diffusivity across the skin

dC/ds - concentration gradient across the skin, J^e is the flux due to electric current facilitation and is defined by:

$$J^e = [(Z_i D_i F) / R T] C_i dE / ds$$

C_i - donor concentration of the ionic species I, Z_i - electric valence of ionic species I, D_i - diffusivity of ionic species in the skin, F - Faraday constant
 T - absolute Temperature, R - gas constant
 dE/ds - electric potential gradient across the Skin, J^c is the flux due to connective transport and is defined by:

$$J^c = k C S I_d$$

k - proportionality constant, C - concentration in the skin tissue, I_d - current density

Advantages

Advancement of a non invasive iontophoretic drug delivery technique for the transdermal controlled administration of drugs through unbroken skin for systemic medication can potentially achieve one or more of the following benefits.

- Avoids the risk and inconveniences of parenteral therapy.
- Delivery of ionized as well as unionized molecules.
- Easy termination of drug delivery in case of toxicity.
- Offering better control over the quantity of drug delivered since the amount of drug delivered depends on applied current, duration of applied current, and area of skin exposed to the current.
- Prevent variation in the absorption and metabolism as seen with oral administration.
- Reducing significantly inter and intra-individual variability since the rate of drug

delivery is more dependent on applied current than on stratum corneum characteristics.^{11,12}

- Utilization of drug candidate with short biological half life and narrow therapeutic index.¹⁰
- Decreases the total dose and dosing frequency.
- Restoration of the skin barrier property without producing severe skin irritation.
- Facilitate continuous or pulsatile delivery of drug. (depending on the current applied)
- Enhancing the delivery of polar molecules as well as high molecular weight compounds.
- Simple non invasive administration and improved bioavailability.
- Enhanced safety, efficacy, reliability and acceptability.
- **Disadvantages**
- Cannot deliver drug by iontophoresis if drug causes irritation.
- There is a limit to the amount of medication that can be delivered usually 5 to 10mg/hr.
- Some drugs cause long lasting pigmentation after iontophoretic application.
- During iontophoretic transport across the skin, the drug encounters potential of hydrogen (pH) differences between 4 to 7.3, leading to the possibility of the drug molecule becoming uncharged and losing the major effect of electric field.
- Increasing the current strength or applications for longer periods can lead to pain, burning sensation, blister formation and skin necrosis.¹³
- Iontophoresis is not suggested for under arm or facial / head hyperhidrosis.
- Iontophoresis cannot achieve high drug level in blood.
- Diseased skin as well as extent of disease can affect penetration.
- The metabolic enzyme in the skin can increase the problem.
- Iontophoresis is restricted to drugs that can be formulated in ionized form.¹⁴

Principle

This technique is based on the principle that application of electric field provides external force to drug ions for passage across the skin, thereby enhancing drug permeability through the membrane.¹⁵

Iontophoresis enhance the penetration of electrically charged drugs into surface tissues by the application of an electric current.¹⁶ 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”. Shown in Figure No.1

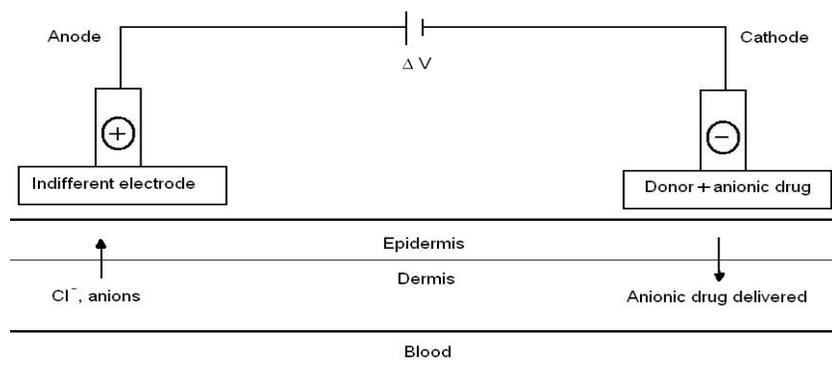


Fig. 1: Iontophoretic technique

Anodal and iontophoresis

If delivery of a positively charged drug is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode. On application of an electromotive force the drug is repelled and travels across the stratum corneum towards the cathode, which is placed elsewhere on the body. Communication between the electrodes along the surface of the skin has been shown to be negligible.¹⁷

Cathodal iontophoresis

On application of an electromotive force the drug is repelled and travels across the stratum corneum towards the anode, which is placed elsewhere on the body.

Mechanism of iontophoresis:

Different possible compound penetration mechanisms were studied and hypothesized for iontophoretic application on skin. Iontophoresis enhances transdermal drug delivery by various mechanisms,

- **Electromigration / Electrorepulsion:** Ion electric field interaction provides a repulsive force that drives ions through the skin.
- **Applied electric current:** Electric current alter the molecular arrangement of skin component. This alteration could yield some change in the skin permeability.
- **“Flip-flop” gating:** This theory is based on the hypothesis that the skin permeability is changeable through the induction of electric current.^{18, 19, 20, 21, 22} When an electric current is applied across a cellular membrane a voltage-dependent “flip-flop” of polypeptides

helices occurs. This causes a rearrangement of the helices to a parallel fashion. i.e. voltage dependent pore formation in the stratum corneum occurs. Pores are thus opened up as a result of the repulsion between neighboring dipoles and water molecule and ions will flow in the pore channel to neutralize the dipole moments. This phenomenon should lead to an enhancement in skin permeability for peptide and protein molecules and other charged molecules.

- **Electroosmosis / Convective force:** Electroosmosis produces bulk motion of solvent that carries ions or neutral molecules with the solvent stream. The skin is negatively charged at pH values above 4, implying that positively charged moieties like Na⁺ ions will be more easily penetrated as they attempt to neutralize the charge in the skin to maintain electroneutrality. Thus the transfer of ions under physiological conditions is from the anode to the cathode. For loss of each cation (sodium ion) from the electrode in this process, a counter ion, i.e. an anion, Cl⁻ moves in the opposite direction from the cathode to the anode.
- **Transport number of ion:** Which describes the fraction of the total current transmitted by the ion and depends on the physicochemical properties of the respective ions. Na⁺ is greater than Cl⁻ and also the skin facilitates movement of Na⁺ more than Cl⁻, hence there is a net increase in the NaCl in the cathodal segment and net decrease in NaCl on the anodal side. Due to this electrochemical gradient, osmotic flow

of water is induced from the anode to the cathode. If any neutral drug molecules are present at the anode at this time they can be convected through the skin along with the water. Such water movement often results in pore shrinkage at the anode and pore swelling at the cathode.²³

- **Concentration gradient:** Concentration gradient and electrochemical gradient developed across the skin also enhance the drug transport.
- **Pathway of drug transport in iontophoresis**
- This ion transfer was first demonstrated by Morton in 1898.²⁴ More recent studies^{25, 26, 27, 28, 29} have used the electric current traverses the skin by passing primarily through already existing pathway in the skin mainly:
- **Transappendageal:** This includes hair follicles and sweat glands which are the major pathway of drug transport.³⁰ This was demonstrated by Cullander and Guy,³¹ who used vibrating probe electrodes to recognize site-specific ionic flows occurring in hairless mouse skin.
- **Paracellular transport:** Water and uncharged polar solute transported through this pathway.³²
- **Artificial shunts:** Artificial shunts are formed due to temporary distraction of the organized structure of the stratum corneum.
- **Temporary pore formation:** A temporary pore formation due to 'flip-flop' movement in the polypeptide helices in the stratum corneum.
- Other factors such as the source and structure of skin and the density of hair follicles will contribute to the determination of the transport pathways.

FACTORS AFFECTING IONTOPHORESIS

Many factors have been shown to affect the result of iontophoresis they are:

Physicochemical properties

Various physicochemical properties like charge, molecular size, potency and solubility, species variation of drug affects iontophoresis.

- **Potency:** The dose of drug given through iontophoresis must be low.
- **Charge:** The effect of ionic charge of drug molecules on iontophoresis was observed that monovalent molecules could be delivered more easily than divalent ones, even if they had similar molecular weight.

This suggests that divalent ions may interact more strongly with charged sites in the skin than monovalent, there by resulting in a slower migration.^{33, 34}

- **Solubility:** The drug must have good partition coefficient.
- **Molecular size:** As small molecules are more mobile than large molecules hence, they are
- easily transported by iontophoresis but large molecules are also iontophoresable.
- **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.
- **Formulation factor**
- **Drug pH:** Iontophoresis is a procedure of ion movement forced through the application of an electric field. Thus the optimum pH for iontophoretic delivery is where the compound exists mainly in its ionized form.^{35, 36} Iontophoretic transport of lidocaine was found to be highest at pH 8.5, where the molecule exists mainly in the ionized form.^{37, 38, 39}
- The pH affects iontophoresis in three ways,
- **Drug concentration:** Increasing drug concentrations results in greater drug delivery to a certain degree. At higher concentrations, it is possible that the transport becomes independent due to saturation of the boundary layer in relation to the donor solution. If the concentration of ions in a solution is too great, it causes a bottleneck effect as the ions attempt to pass through the available pores.^{40, 41}

2. Ionic strength: If buffer ions are included, they compete with the drug for the delivery, decreasing the quantity of drug delivered, especially since buffer ions are generally smaller and more mobile than the larger active drug.

3. Viscosity: The migration of drug is inversely related to the viscosity.

Physiological Factors: Physiological factors which involves the skin on which the electrode is placed. Factors like its thickness presence or absence of pores, its permeability affects the iontophoretic

transport. Sweat glands are most significant route for the conduction of electric charge into the skin.⁴²

Experimental factors

Type of electrode: The type of electrode used also affects the iontophoretic drug delivery system Ag/AgCl electrode are most preferred electrode as they resist the change in pH which are generally seen during the use of platinum or zinc chloride electrode.



After the completion of circuit an insoluble AgCl precipitate at the anode electrode.

Continuous and pulsatile current: Chien et al. suggested that if direct current is applied in continuous manner to the stratum corneum to facilitate the transport of charged molecules, an electro chemical polarization occurs in the skin, which results in the reduction in the transport of drug molecules, which ultimately decrease of efficiency of iontophoretic drug delivery system. To avoid this, the current must be applied in pulsatile manner, which is termed as pulsed direct current (D.C.). In pulse D.C., the electric current is switched "on" and "off" periodically. In the state of "on" charged drug are delivered by the iontophoresis process into the skin. In the state of "off" where the stimulation is removed to permit the skin a chance to depolarize.

Duration and intensity of current: The strength of current used also depends on the sensitivity of the patient. It is desired to increase the current slowly and to remain at a predetermined level as long as the treatment required, following which the current is slowly decreased to zero. The time for iontophoresis ideally is 1 minute for increasing phase and 30 seconds for the decreasing phase. The intensity of current used is between 40mA to 10mA regulated with a 2500 Ω potentiometer. Current ranging from 5 to 10mA has been found to be painless.

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 Nerst-Planck equation. It states that the flux of the ionic drug due to applied electric field is directly proportional to the voltage drop and charge of the ion. The enhancement factor for hairless mouse skin showed good agreement up to 0.5 volts and significantly higher at 1.0 volt due to skin damage but it is up to 0.25 V.

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.

On/Off Ratio: The on/off ratio of electricity affects the relative proportion of polarization and depolarization of skin, which results the efficiency of transdermal iontophoretic drug delivery. The number of on/off cycles in each second is shown as frequency. For example the on/off ration 1:1 at frequency 2000 Hzs (0.5 ms/cycle) provides 0.25 ms depolarization period and same time for the polarization.

APPLICATION OF IONTOPHORESIS

Iontophoretic drug delivery system is suitable for the delivery of a wide range of molecules, such as 5-fluorouracil, apomorphine, buspirone hydrochloride, rotigotine, sumatriptan.

Monitoring of glucose

As we have seen, electro osmosis is one of the mechanism of iontophoresis which can be used for non invasive monitoring of glucose. As the flow of glucose is in opposite direction i.e. in opposite direction in skin to conventional iontophoresis, called as reverse iontophoresis.⁴³ This property along with in situ glucose sensor has been used in Gluco Watch® Biographer (Cygnus Inc., Redwood City, CA, USA)⁴⁴ The wrist watch device contains sampling and detecting units, electronic circuitry and a digital display. At pH 4 the skin is negatively charged, the sodium ions move from the anode towards cathode and creates a conventional flow along with glucose is transported which is oxidized by glucose oxidase to release hydrogen peroxide, this is then detected by the device.⁴⁵ This device allows noninvasive extraction of glucose across the skin, allowing a diabetic's glycemia to be evaluated every 10 min. over several hours.

Topical delivery

By varying the current strength we can control the delivery rates of drugs makes iontophoresis an alternative technique for topical delivery. Yamashita et al. studied the efficacy of iontophoretic delivery of calcium for treating hydrofluoric acid induced burns on rat.⁴⁶ The burn was induced by using 50% hydrofluoric acid. The result of experiment is that the burn areas were significantly reduced by iontophoresis more than any other mode of calcium administration by topical or injection therapy.

Delivery of antisense oligonucleotides

Oligonucleotides are usually given by injection and hence iontophoresis is an alternative route for systemic delivery. The transdermal route is attractive because it may enable the localized delivery of the oligonucleotide which is desirable for condition like dermatitis. Antisense oligonucleotide binds to the mRNA of the disease causing genes and inhibits the synthesis of disease related proteins. Sakamoto et al.⁴⁷ conducted a study which includes the topical delivery of an antisense oligonucleotide for mouse IL-10 over expansion which is one of the important pathogenic factors in skin lesions resulting from

atopic dermatitis (AD). By using iontophoretic delivery the author were able to deliver 30% of the applied dose locally to the dermis and epidermis. Iontophoretic delivered oligonucleotides decreased the level of mRNA and protein of IL-10 in lesions of mice. In addition a number of studies have been demonstrated measurable concentrations of oligonucleotides with in vitro and in vivo delivery.^{48, 49}

Treatment of hyperhidrosis

One of the most successful application of Iontophoresis is for the treatment of hyperhidrosis.^{50, 51, 52} Hyperhidrosis is a situation that most often results in excessive sweating in hand and feet. Tap water iontophoresis is one of the popular treatment used in this condition. Other conditioning medium like anticholinergic compounds e.g., Atropine⁵³, glycopyrronium bromide⁵⁴, poldine methyl sulphate⁵⁵ have a long lasting effect than water, but the side effect of systemic anticholinergic blockade have prohibited their wide acceptance. The procedure includes mild electric current that is passed through the tap water to temporarily block the sweat glands. A hand and foot is each placed in a different water basin and the electric current is slowly increased to the required level and maintained for 20 min followed by a gradual decrease.⁵⁶

Dermatological applications: Iontophoresis is used for the treatment of various dermatological conditions like

Viral infections (Herpes simplex): The treatment of herpes simplex by iontophoretic application of idoxuridine was reported by Gangarosa.⁵⁷ Relief of discomfort and reduction of healing time of herpes simplex lesions by Iontophoretic treatment with idoxuridine is reported by Leaks.

Lichen planus: The treatment of erosive lichen planus, with methyl prednisolone was reported by Gangarosa.⁵⁸

Aphthous stomatitis: The treatment of aphthous stomatitis with 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.⁵⁹

Warts: The treatment of warts with sodium salicylate iontophoresis has been reported.⁶⁰

Fungal infection: The successful treatment of dermatophytosis with the use of copper sulphate Iontophoresis⁶¹ and of sporotrichosis with potassium iodide iontophoresis has been reported.⁶²

Ulcers: The treatment of ischemic leg ulcers with histamine iontophoresis was reported by Abramson et al.⁶³

Protein and peptide delivery: This is one of the important application of iontophoretic drug delivery system. The delivery of micromolecules like peptides, which are often polar, carry a charge and cannot be

administered via oral route due to poor absorption and degradation. Thus, iontophoretic delivery itself offers the advantage of bypass first pass metabolism and gastrointestinal degradation.

Miscellaneous use

Lymphedema: The successful use of hyaluronidase iontophoresis in the treatment of lymphedema of the limbs.⁶⁴

Sweat test: The diagnosis of cystic fibrosis by the sweat test with pilocarpine iontophoresis has been reported.⁶⁵

Scleroderma: Hyaluronidase iontophoresis led to increase the skin softness and flexibility of tissue and decreased cold sensitivity.⁶⁶

Vitiligo: Iontophoresis of 1% meladine solution in patient with vitiligo showed marked repigmentation.⁶⁷

Synergistic Effect of other Enhancers with iontophoresis:

Various other physico-chemical penetration enhancers are used other than iontophoresis that includes ultrasound, chemical enhancers, and electroporation have been used for enhancing transdermal drug transport. The following combinations of iontophoresis with other techniques have been used for transdermal drug delivery: i) Iontophoresis + Chemicals ii) Iontophoresis + Ultrasound iii) Iontophoresis + Electroporation.

1. Iontophoresis and chemical enhancer

Iontophoresis enhances transdermal drug delivery via electrorepulsion, electroosmosis, or enhanced diffusion. On the other hand, chemical enhancers increase transdermal drug delivery via several different mechanisms, including increased drug solubility, increased drug partitioning into the Stratum corneum fluidization of lipid bilayers, and disruption of the intracellular proteins.^{68, 69, 70} Oh et al. reported that propylene glycol and oleic acid enhances transdermal transport of AZT synergistically in combination with iontophoresis. Application of propylene glycol and oleic acid enhances transdermal flux of AZT by about 200-fold. On the other hand, application of iontophoresis alone enhances AZT flux by 7-fold. However, the combination of propylene glycol and iontophoresis enhances AZT flux by about 400-fold.

2. Iontophoresis and Ultrasound:

Synergy between ultrasound and iontophoresis is predictable, since these enhancers increase transdermal transport through different mechanisms. The synergistic effect of ultrasound and iontophoresis on transdermal transport was attributed to ultrasound-induced structural changes in the skin. Application of ultrasound should disorder the lipid bilayers of the skin, thereby introducing

new transport pathways. Both the effect of iontophoresis and ultrasound result in enhancement of transdermal drug delivery.^{71,72}

Le et al. performed a research using a model drug, heparin. Ultrasound was applied only once to each skin piece (along with 1% solution of dodecyl pyridinium chloride) for about 10 minutes prior to application of iontophoresis. The enhancement of heparin flux due to ultrasound and iontophoresis treatment was about 56-fold applied only for 1 hour. This enhancement was higher than the sum of those obtained during ultrasound alone (3-fold) and iontophoresis alone (15-fold). Thus, the effect of ultrasound and iontophoresis on transdermal heparin transport is truly synergistic.

3. Iontophoresis and Electroporation

The mechanism for the synergistic effect of iontophoresis and electroporation is likely to be similar to that of iontophoresis and ultrasound. Electroporation may create new transport pathways in the stratum corneum, thus assist the passage of current during iontophoresis. The device requirements are also likely to be comparable to those for electroporation alone. Chang et al. studied the effect of iontophoresis and electroporation on transdermal delivery of salmon calcitonin and parathyroid hormone through human epidermis.⁷³ The authors state that a combination of electroporation and iontophoresis induced higher transdermal permeation than that induced by either one technique alone. Specifically, transdermal calcitonin fluxes due to electroporation alone or iontophoresis alone were respectively < 20 ng/cm²/hr and about 200 ng/cm²/hr. However, application of electroporation prior to iontophoresis increased calcitonin flux to about 800 ng/cm²/hr. Electroporation also shortened the lag time of iontophoretic transdermal delivery of salmon calcitonin.

CONCLUSION

Iontophoretic drug delivery systems form a major group of the relatively less physical enhancement transdermal delivery systems that have been successfully developed and commercialized. The electrically driven penetration enhancement provided by this method has succeeded in overcoming the formidable barrier presented by the stratum corneum has shown to be a promising technique for various agents including macromolecules. Iontophoresis has been explored for many dermatological and other medical conditions with reports of considerable success. The iontophoretic delivery of macromolecules will open the doors to non-invasive transdermal delivery of peptide-based pharmaceuticals, the advances in recombinant DNA technology, which are the wonder drugs of tomorrow. However, more rigorous studies are needed to investigate the application of this method of therapy.

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