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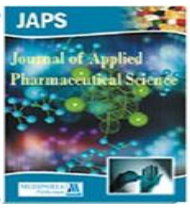


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# Iontophoretic drug delivery: History and applications

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## ABSTRACT

The goal of delivery system is to get optimal therapeutic management. But, it still remains a challenge in the field of pharmaceuticals for delivery of ionic species and some non ionic. Several transdermal approaches have been used and recently there has been a great attention in using iontophoretic technique for the transdermal drug delivery of medications, both ionic and non ionic. This technique of facilitated movement of ions across a membrane under the influence of an externally applied electric potential difference is one of the most promising physical skin penetrations enhancing method. The payback of using iontophoretic technique includes improved systemic bioavailability ensuing from bypassing the first metabolism. Variables due to oral administration, such as pH, the presence of food or enzymes and transit times can all be eliminated. This article is an overview of the history of iontophoresis, mechanism, principles and factors influencing iontophoresis and its application for various dermatological conditions.

***Key words***: Iontophoresis, Penetration, skin, Topical drug delivery, Transdermal drug delivery etc.

## INTRODUCTION

Currently the transdermal route has become one of the most successful and innovative focus for research in drug delivery, with around 40% of the drug candidate being under clinical evaluation related to transdermal or dermal systems. The technology has a proven record of FDA approval since the first transdermal patch was approved in 1981(Langer, 2004). Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications (Front Line Strategic Consulting Inc., 2002). The benefits of using transdermal drug delivery include improved systemic bioavailability resulting from by passing the first metabolism. Variables due to oral administration, such as pH, the presence of food or enzymes and transit times can all be eliminated. In the development of new transdermal drug delivery devices the object is to obtain controlled, predictable and reproducible release of drugs into the blood stream of the patient. The transdermal device acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug flux is controlled by the device instead of the skin, delivery of the drug is more reproducible leading to smaller inter and intrasubject variations, since the drug release from the device can be controlled accurately than the permeability of the skin (Guy et al., 1992). Despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues for transdermal products are shared between the USA at 56%, Europe at 32% and Japan at 7%. In a recent market report it was suggested that the growth rate for transdermal delivery systems will increase 12% annually through to 2007 (Front Line Strategic Consulting Inc., 2002).

An increasing number of TDD products continue to deliver real therapeutic benefit to patients around the world (Masada T et al., 1989). More than 35 TDD products have now been approved for sale in the US, and approximately 16 active ingredients have been approved for use globally. Statistics reveal a market of $ 12.7 billion in the year 2005 that is expected to increase to $ 21.5 billion in the year 2010 and $ 31.5 billion in the year 2015(Langer R., 2004 and Masada T et al., 1989). Several transdermal approaches have been used and recently there has been a great attention in using iontophoretic technique for the transdermal drug delivery of medications, both ionic and non ionic. The method of iontophoresis was described by *Pivati in 1747*. Galvani and Vota two well known scientists working in the 18th century combined the knowledge that the electricity can move different metal ions and the movement of the ions produce electricity. The method of administering pharmacological agents by iontophoresis became popular at the beginning of 20th century due to the work of Leduc (1900) who introduced the term iontotherapy and formulated the laws for this process (Green PG et al., 1993). 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 (Masada T et al., 1989 and Srinivasan V et al., 1989). Transdermal iontophoretic technique is capable of administering drugs in a pulsatile pattern by alternately applying and terminating the current input at programmed rate (Singh P et al., 1994). In addition, delivery rate can be controlled by the intensity of applied electric current or Electro-chemical potential gradient (Lelawong P et al., 1990). It can also be define as a means of enhancing the flux of ionic drugs across skin by the application of an electrochemical potential gradient (Kanikkannan N., 2002). Iontophoresis, which is the facilitated movement of ions across a membrane under the influence of an externally applied small electrical potential difference (0.5 mA/cm2 or less), is one of the most promising novel drug delivery system, which has proved to enhance the skin penetration and the release rate of a number of drugs having poor absorption / permeation profile through the skin (Green et al., 1993, Tyle, 1986, Green, 1996 and Sage, 1993). Recently, Bos and Meinardi introduced us to the 500 Dalton rule for skin penetration of chemicals and drugs (Jaskari et al., 2001).

## HISTORICAL BACKGROUND

In 1747 publication, the Italian librarian Giovanni Francesco Pivati (1689 –1764) reported that the smell of Peruvian balsam hermetically sealed in a glass cylinder became apparent in the room after applying electrical current and could even be transmitted to another room by a wire (Helmstädter, 2001). Other observations described by Pivati refer to an increased intensity of the smell of flowers by electrifying the vase and to the symptoms typical for mercury intoxication of a patient holding electrified mercury containing glass cylinder in his hands. After Alessandro Volta found a simple method of producing a continuous flow of current (the Voltaic pile) in 1800, attempts to transmit chemical entities through membranes were made again.

**Table 1:** Iontophoretic treatment between 1800 and 1900 (Helmstädter A., 2001).

| Scientist | Year of report | Drugs used |
|---|---|---|
| Richardson | 1858 | Chloroform/aconitine |
| Erb | 1884 | Various |
| Wagner | 1886 | Cocaine |
| Boccalari/Manzieri | 1888 | Strychnine, atropine, quinine, KI |
| Lauret | 1885 | Various |
| Adamkiewicz | 1886 | Chloroform |
| Lambroso/Matteini | 1886 | Chloroform |
| Corning | 1886 | Cocaine |
| Peterson | 1888/1889 | Cocaine |
| McGraw | 1888 | Cocaine |
| Cagney | 1889 | Potassium iodide |
| Edison | 1890 | Lithium salts |
| Imbert de la Touche | 1891 | Lithium salts |
| Gärtner/Ehrmann | 1892 | Mercury salts |
| Westlake | 1892 | Cocaine/carbolic acid, pyrazone |
| Morton | 1898 | Cocaine |

**Table 2:** Iontophoretic treatment at the end of the 1930's (Helmstädter A., 2001).

| Ions used | Indication |
|---|---|
| Zinc | Wound care, hay fever |
| Copper | Substitute for zinc |
| Silver | Pain relief |
| Chlorine/iodine | Softening of scar tissue |
| Mercury | Syphilitic ulcers |
| Magnesium | Warts |
| Lithium | "Gouty arthritis" |
| Cocaine | Anaesthesia |
| Adrenalin | Vasoconstriction |
| Quinine | Neuritis, neuralgia |
| Histamine | Rheumatic diseases |

Important contributions were made by the French physician Bernard Raymond Fabré-Palaprat (1773–1833). A further milestone in the history of iontophoresis was the "voltaic narcotism", a procedure for dental anesthesia, introduced by Benjamin Ward Richardson ("father of dental iontophoresis", 1828– 1896).In the 1870s, the German Hermann Munk (1839–1912) extensively investigated the current mediated transport of substances through porous membranes (Helmstädter A., 2001). 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 William James Morton (1846-1920), Stephen Leduc (1853-1939) and Fritz Frankenhauser (1868), administration of metal ions as well as alkaloids was tried at that time (Helmstädter A., 2001) [see table 1 & 2]. 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. Inchley also carried out similar experiments in 1921 (Inchley OJ., 1921). The application of iontophoresis to the treatment of hyperhydrosis could be reduced by ion transfer of certain applied solutions by

electro-phoretic technique. Today, the treatment of hyperhydrosis is the most successful and popular applications of iontophoresis in dermatological medication (Sloan JB et al., 1986). The transdermal delivery of many ionized drugs at therapeutic levels is precluded by their slow rate of diffusion under a concentration gradient alone are now application with the help of iontophoretic technique and devices (Inchley OJ., 1921 and Wang Y et al., 2005).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 (Sage BH., 1993, Wang Y et al., 2005 and Rawat S et al., 2008). America's first commercially marketed transdermal patch used a passive mode of drug delivery that permitted the drug to diffuse through a vascular 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. While passive transdermal technology grows in popularity, all the available transdermal delivery systems use passive technology. Passive technology has always depended on the physicochemical properties of the drug candidate, large molecule drugs, such as, proteins and peptides, could not be considered. But, advances in the research have led to a better understanding of the physiology of the skin and more familiarity with the drug transport characteristics (Rawat et al., 2008).

**Table 3:** Recent studies and applications of iontophoresis (since approx. 1950) (Helmstädter A., 2001).

| Scientist | Drug | Indication |
|---|---|---|
| Popkin et al. | Hyaluronidase | Scleroderma |
| Schwartz et al | Hyaluronidase | Lymphoedema |
| Coyer | Citrate | Rheumatic arthritis |
| Stolman | Various | Hyperhidrosis |
| Rosenstein et al | Various | Pain relief |
| Albrecht | Vincristine | Trigeminal neuralgia |

## IONTOPHORESIS

The highly lipophilic nature of the skin restricts the permeation of hydrophilic, high molecular weight and charged compounds through the stratum corneum into the systemic circulation. However, many therapeutically active drug molecules are hydrophilic and possess high molecular weights for example, peptides (Sloan et al., 1986 and Williams et al., 1992). Iontophoresis simply defined is the application of an electrical potential that maintains a constant electric current across the skin and enhances the delivery of ionized as well as unionized moieties (Williams et al., 1992). This technique is capable of expanding the range of compounds that can be delivered transdermally. Along with the benefits of bypassing hepatic first pass effect, and higher patient compliance, the additional advantages that the iontophoretic technique offers can be summarized as follows (Williams et al., 1992, Williams et al., 1991 and Glikfeld et al., 1988).

- Delivery of both ionized and unionized drugs.
- Depending on the current applied it is enabling continuous or pulsatile delivery of drug.
- Permitting easier termination of drug delivery.
- Offering better control over the amount of drug delivered since the amount of compound delivered depends on applied current, duration of applied current, and area of skin exposed to the current.
- Restoration of the skin barrier functions without producing severe skin irritation.
- Improving the delivery of polar molecules as well as high molecular weight compounds.
- Ability to be used for systemic delivery or local (topical) delivery of drugs.
- Reducing considerably inter and/ or intra subject variability in view of the fact that the rate of drug delivery is more dependent on applied current than on stratum corneum characteristics.

### Principles of iontophoresis

The iontophoretic technique is based on the general principle that like charges repel each other. Thus during iontophoresis, if delivery of a positively charged drug (DC) 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 moves 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 (Glikfeld et al., 1988) , i.e. movement of the drug ions between the electrodes occurs through the skin and not on the surface. When the cathode is placed in the donor compartment of a Franz diffusion cell to enhance the flux of an anion, it is termed cathodal iontophoresis and for anodal iontophoresis, the situation would be reversed. Neutral molecules have been observed to move by convective flow as a result of electro-osmotic and osmotic forces on application of electric current (Green et al.,1993).

Electromigration of ions during iontophoresis causes convective solvent motion and this solvent motion in turn ‘drags’ neutral or even charged molecules along with it. This process is termed as electro-osmosis. At pH values above 4, the skin is negatively charged, implying that positively charged moieties like $Na^+$ will be more easily transported as they attempt to neutralize the charge in the skin to maintain electroneutrality (Burnette et al., 1987). Thus the movement of ions under physiological conditions is from the anode to the cathode. For loss of each cation (sodium ion in this case) 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. It is the transport number of each ion, which describes the fraction of the total current transferred by the ion and depends on the physicochemical properties of the respective ions. $t^+_{Na}$ is greater than $t^-_{Cl}$ and also the skin facilitates movement of $Na^+$ more than $Cl^-$, hence there is a net increase in the NaCl in the cathodal compartment 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 transported through the skin along with the water. Such water movement often results in pore shrinkage at the anode and pore swelling at the cathode (R. Harris., 1967).

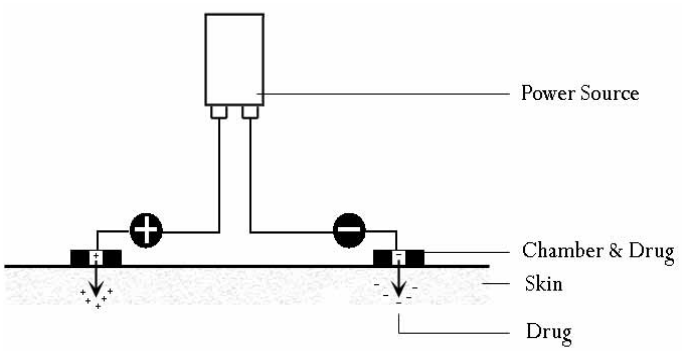


**Fig. 1:** Principle of Iontophoresis (http://www.dcu.ie/~ best/ idd .html)

## Merits

1. It is a non-invasive technique could serve as a substitute for chemical enhancers (Srinivasan et al., 1989).
2. It eliminates problems like toxicity problem, adverse reaction formulation problems associated with presence of chemical enhancers in pharmaceuticals (Bellantone et al., 1986).
3. It may permit lower quantities of drug compared to use in TDDS, this may lead to fewer side effects (Bodde et al., 1989).
4. TDDS of many ionized drug at therapeutic levels was precluded by their slow rate of diffusion under a concentration graduation, but iontophoresis enhanced flux of ionic drugs across skin under electrical potential gradient (Srinivasan et al., 1989).
5. Iontophoresis prevent variation in the absorption of TDDS (Bodde et al., 1989).
6. Eliminate the chance of over or under dosing by continuous delivery of drug programmed at the required therapeutic rate (Bodde et al., 1989).
7. Provide simplified therapeutic regimen, leading to better compliance (Phipps et al., 1989).
8. Permit a rapid termination of the modification, if needed, by simply by stopping drug input from the iontophoretic delivery system (Bodde et al., 1989).
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, eg. Thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, interferons, enkaphaline, etc (Phipps et al., 1989).
10. Provide predictable and extended duration of action (Bodde et al., 1989).
11. Reduce frequency of dosage (Yogeshvar et al., 2004).
12. Self-administration is possible (Yogeshvar et al., 2004).
13. A constant current iontophoretic system automatically adjust the magnitude of the electric potential across skin which is directly proportional to rate of drug delivery and therefore, intra and inter-subject variability in drug delivery rate is substantially reduced. Thus, minimize inter and intra-patient variation (Yogeshvar et al., 2004).
14. An iontophoretic system also consists of a electronic control module which would allow for time varying of free-back controlled drug delivery (Yogeshvar et al., 2004).
15. Iontophoresis turned over control of local anesthesia delivery in reducing the pain of needle insertion for local anesthesia (Bellantone et al., 1986).
16. By minimizing the side effects, lowering the complexity of treatment and removing the need for a care to action, iontophoretic delivery improve adherence to therapy for the control of hypertension (Zakzewski et al., 1991).
17. Iontophoretic delivery prevents contamination of drugs reservoir for extended period of time (Padmanabhan et al., 1990).

## Demerits

1. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate (Sanderson et al., 1989).
2. An excessive current density usually results in pain (Sanderson et al., 1989).
3. Burns are caused by electrolyte changes within the tissues (Moliton et al., 1939).
4. The safe current density varies with the size of electrodes (Moliton et al., 1939).
5. The high current density and time of application would generate extreme pH, resulting in a chemical burn (Miller et al.,1987).
6. This change in pH may cause the sweat duct plugging perhaps precipitate protein in the ducts, themselves or cosmetically hyperhydrate the tissue surrounding the ducts (Sanderson et al., 1989).
7. Electric shocks may cause by high current density at the skin surface (Miller et al.,1989).
8. Possibility of cardiac arrest due to excessive current passing through heart (Padmanabhan et al., 1990).
9. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery (Padmanabhan et al., 1990).
10. High molecular weight 8000-12000 results in a very uncertain rate of delivery (Moliton et al., 1939).

**Table 4:** Factors affecting iontophoretic delivery of the drug

| Name of the factors | | | |
|---|---|---|---|
| **Physiochemical Properties** | **Drug formulation** | **Experimental factors** | **Biological factors** |
| Molecular size | pH | Current strength | Intra and inter subject variability |
| Molecular weight | Ionic strength | Current density | |
| Charge | Presence of co-ions | Pulsed current | Regional blood flow |
| Polarity | | Duration of application | Skin pH |
| Concentration | | Electrode materials | Condition of skin |

## PHYSIOCHEMICAL PROPERTIES

### Molecular size and molecular weight

The molecular size of the solute is a major factor governing its feasibility for iontophoretic delivery and hence the amount transported. When the iontophoretic delivery of carboxylate ions was studied, flux for acetate was found to be more than that of hexanoate and dodecanoate. This suggests that smaller and more hydrophilic ions are transported at a faster rate than larger ions (Miller et al., 1987 and Miller et al., 1989), 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 (Chien et al., 1989). Many studies correlating flux as a function of molecular weight have been conducted and it was concluded that for electro repulsive iontophoresis, when all other conditions were kept constant, transport of compounds decreased with increase in molecular weight (chloride> amino acid >nucleotide > tripeptide >insulin) (Green et al., 1991, Green et al., 1992, Langkjaer et al., 1994, Vander-Geest et al., 1996 and Burnett et al., 1987).

### Charge

Charge on a molecule is an important physicochemical property governing iontophoretic transport, since the sign of the charge determines the mechanism by which iontophoresis will proceed e.g., electrorepulsion and electroosmosis (Berner et al ., 1998). Although the transport of cations has been shown to be better than anions for amino acids and peptides (Green et al., 1991,Green et al., 1992 and Green et al., 1992), this however is not so simple because an increase in charge will require pH to be decreased, which in turn shall directly decrease the electroosmosis and electrotransport process. An increased positive charge on peptide, cause it to bind tightly to the membrane creating a reservoir which in turn can decrease the rate at which the steady state flux will be achieved (Berner et al ., 1998).

### Polarity

Generally, the compounds which are hydrophilic are considered ideal candidates for optimum flux e.g., nalbuphine and its ester showed an increased flux as the lipophilicity of the compound decreased (Sung et al., 2000).

### Concentration

Concentration of drug is one of the most important factors affecting iontophoretic process. The effect of the concentration has been studied on a number of drugs. An increase in concentration was shown to increase the apparent steady state flux of a number of drugs e.g., metoprolol (Thysman et al., 1992), diclofenac sodium (Koizumi et al., 1990), rotigotine (Nugroho et al., 2004) and ketorolac (Tiwari et al., 2003). All these drugs showed a proportional increase in flux with an increase in concentration. The concentration dependent iontophoretic delivery has not been fully investigated, some of the authors reported that as the concentration of drugs viz. acetate ions (Idson, 1975) and hydromorphones (Srinivasan V et al., 1990), increase in reservoir system then permeation of drug also increases. O'malley and Oester (1995) showed the flux of solute was non-linearly proportional to its concentration.

## DRUG FORMULATION

### pH

pH is an important factor governing the iontophoretic delivery of drugs (Siddiqui et al., 1985), this affects iontophoresis in two ways. The pH of the donor solution influences the pH of the skin and thus makes the skin a permselective membrane especially if the pH of the skin rises above 4. This causes the carboxylic acid moieties in the skin to become ionized and then the anodal iontophoresis promotes the permeation of cationic drugs. The pH of the donor solution also affects the ionization of the drug itself. Thus a weakly basic drug will be ionized to a lower extent at pH higher than its pKa and will not permeate by electromigration in presence of iontophoresis. The drug will be more dependent on electro-osmosis to travel across the skin (Phipps et al.,1989). Sanderson et. al., suggested that the control of pH offers advantage of polarization effects on skin and enhance the perm selectivity of skin for catecholemine drug during iontophoretic delivery (Phipps et al.,1989). Several authors reported the pH dependent penetration enhancement of insulin (Siddiqui et al.,1987), lidocaine (Siddiqui et al., 1985), enalaprilate (Patel et al., 1990), and acetate ions (Miller et al.,1989).

### 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 (Srinivasan et al.,1989 and Thysman, et al., 1992), and has no significant effect on penetration up to the 0.5 V (Onken et al.,1963).Many peptides widely studied for ionic strength showed a higher flux occurring at low electrolyte concentration (Lelawongs et al.,1989, Morimoto et al.,1992,

Heinsberg et al., 1994, Knoblauch et al.,1993, and Fu, et al.,1993).Similarly, drugs like ketorolac showed increased flux with decrease in ionic strength (Tiwari et al.,2003).

**Presence of co-ions**

An ion of equal charge but of different type is referred as a co-ion. The buffering agents used to maintain pH of the donor medium is a source of co-ions. These co-ions are generally more mobile and smaller in size than the drug ions (Bumette et al.,1988). The presence of a co-ion (ion with the similar charge as the drug) results in competition between the drug and the co-ion, a reduction of the fraction of the current carried by the drug and thus a reduction in the transdermal iontophoretic flux of the drug. Nugroho et al. compared the transdermal iontophoretic permeation of rotigotine in presence of three different co-ions: $Na^+$, tetra ethyl ammonium ($TEA^+$) or tetra butyl ammonium ($TBA^+$) at pH 5 and 6 (Nugroho AK et al., 2004). The iontophoretic flux of rotigotine was lower in presence of $Na^+$as compared to $TEA^+$ and TBAC which can be attributed to the higher mobility of the sodium ion due to its lower molecular weight. Replacing $Na^+$ by the larger co-ion $TEA^+$resulted in an increase of the rotigotine flux both at pH 5 and 6 (Idson ,1975).

## EXPERIMENTAL FACTORS

**Current strength**

Current can easily be controlled by the use of electronics, it is a convenient mean to control delivery of drugs to the body (Singh et al.,1997). There is a linear relation between the observed fluxes of a 1-cm $^2$; 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) increased (Abramowitz et al.,1946 and Schriber , 1975). In general, 0.5 mA/cm2 is often stated to be the maximum iontophoretic current which should be used on human beings (Banga,1998).

**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 (Bumette et al.,1988).

**Pulsed current**

The continuous use of direct current (DC), proportional to time, can reduce the iontophoretic flux because of its polarization effect on the skin (Lawler et al.,1960). This can be overcome by the use of pulsed DC which is a direct current delivered in a periodic manner (Banga et al.,1988). During “off stage” the skin gets depolarized and returns to the initial polarized state. However, Bagniefski and Burnett showed that enhanced skin depolarization can decrease the efficiency of drug transport, if the frequency of pulsed current is very high (Bagniefski et al.,1990).

**Duration of application**

The transport of drug delivery depends on the duration of current applied in iontophoretic drug delivery (Abramowitsch et al.,1946).The iontophoretic penetration of drug linearly increased with increasing application time.The skin permeation of arginine vasopressin achieves higher plateau rate and in case of insulin delivery, 2-3 fold reduced the blood glucose levels with increase in duration of iontophoretic application (Chien et al., 1989).

**Electrode materials**

The electrode materials used for iontophoretic delivery are to be harmless to the body and sufficiently flexible to apply closely to the body surface. The most common electrodes are aluminum foil, platinum and silver/silver chloride electrodes used for iontophoretic drug delivery (Molitor ,1943 and Molitor et al.,1939). The type of electrodes used also affect the iontophoretic delivery. Electrodes Ag/AgCl are the most preferred as they resist the changes in pH which are generally seen during the use of platinum or zinc/zinc chloride electrodes. The following reactions typically occur at the anode (Phipps et al.,1989).

$$Ag+Cl^- - AgCl+e^-$$

The electron is released to the circuit and insoluble AgCl precipitates at the anode surface. In the case of other metals like platinum, the chloride ion at the anode will be converted to $Cl_2$ which will in turn react with water to generate hydronium ions. These then migrate to the donor solution and compete with similar-charged drug ions and being highly mobile enter the skin thus reducing drug transport and simultaneously causing skin irritation. The positioning of electrodes in reservoir depends on the charge of the active drug. The distribution of drug within the skin depends on the size and position of electrodes. They are usually selected according to individuals needs. Larger electrode areas introduce the greater amounts of drug but lesser current density is tolerated to the skin in a non-linear manner. Metal electrodes touching to the skin produce burns with much lower current in composition to padded electrodes. A loose contact between the padded electrode and skin also produce burn due to uneven distribution of current. The safe current density varies with the size of electrodes (Molitor,1943 and Molitor et al.,1939).

## BIOLOGICAL FACTORS

**Intra and inter subject variability**

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 (Gangarosa et al., 1978).

**Regional blood flow**

During iontophoresis, the dermal blood supply determines the systemic and underlying tissue solute absorption. Blood supply however, does not appear to affect the drug penetration fluxes through the epidermis during iontophoretic delivery. Cross and Roberts (1995) showed that solute in the upper layer of the skin following iontophoresis was comparable in anaesthetized rats and sacrificed rats. It can thus be presumed that the blood did not affect the penetration through the epidermis since the latter has no blood supply.

**Condition of skin**

In iontophoresis, skin condition also affects the penetrating properties of permeant. Roberts *et al*., studied the *in vivo* passive diffusion of methyl salicylate using skin from different areas of human body and observed the following rank order: abdomen> forearm> instep> heel> planter, for all subjects (Roberts et al., 1982). Feldman *et al*,(1967) showed that the passive diffusion of hydrocortisone occurred maximally from the area with numerous hair follicle while lesser in area with thickest stratum corneum.

**MECHANISM**

The methodologies involved in the currently investigated forms of physical transdermal delivery including: electrically-based techniques: iontophoresis, electroporation, ultrasound, photomechanical wave, structure-based techniques: microneedles and velocity-based techniques: jet-propulsion (Fig. **1**). More formally, transdermal iontophoresis should be called electrically assisted transdermal delivery (Pikal et al.,1990).

The two principal mechanisms by which iontophoresis enhances molecular transport across the skin are:

(a) Iontophoresis, in which a charged ion is repelled from an electrode of the same charge,

(b) Electroosmosis, 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

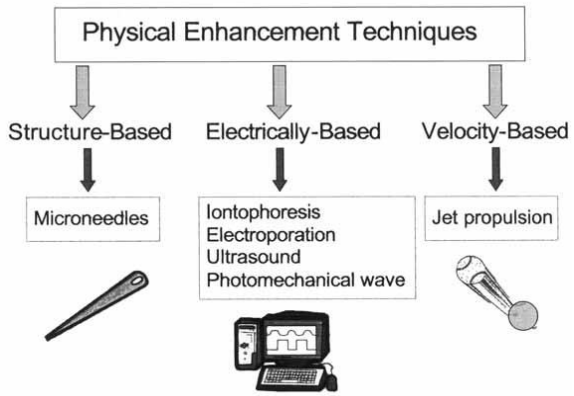


**Fig. 2:** Classification of the types of physical delivery technologies available for transdermal drug application (Roberts et al., 1997).

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The mechanism of iontophoresis is based on the physical phenomenon that “like charges repel and opposite charges attract”. The drugs are forced across the skin by simple electronic repulsion of similar charges. Thus, anionic drugs can cross the skin by using a negatively charged working electrode. Similarly, cationic drugs enter the skin more successfully when a positively charged electrode is used. While delivering a negatively charged drug across biological membrane, it is placed between the negative electrode (cathode), and the skin (Sage, 1993). The drug ion is then attracted through the skin towards the positive electrode (anode) by the electromotive force provided by the cell. In case of positively charged drug, the electrode polarities are opposite. Once the drug has passed through the outer barrier layer of skin, it reaches to its site of action by rapidly going into the circulation. The electric circuit is completed by the movement of endogenous counter ions from within the skin. *In vitro* iontophoretic studies conducted on peptides have shown an increase in the passive permeability of skin post iontophoresis. This shows, that the alteration of the skin barrier function due to current passage *in vitro* is, one of the mechanisms for enhanced permeability following iontophoresis (Green ,1996, Masada et al., 1989 and Inchley, 1921).

Mechanism of iontophoretic transport of drugs across the skin involves either diffusion, migration or electroosmosis. Electroosmosis is the bulk flow of fluid occurring in the same direction as the flow of counter ions when a voltage difference is applied across a charged, porous membrane. This flow involves motion of fluid without concentration gradient and is a significant factor affecting iontophoresis. At physiological pH, human skin has a slight negative charge and counter ions are usually cations. Therefore, flow occurs from anode to cathode electroosmotically thus, enhancing the flux of cationic drugs.

The electrorepulsion effect gives the largest enhancement to the flux of small lipophillic cations (Diego et al., 2001). When the concentration of the ionic drug is very high, so that the drug carries most of the current, electroosmotic flow has a very small effect on the drug flux (Pikal et al.,1990).

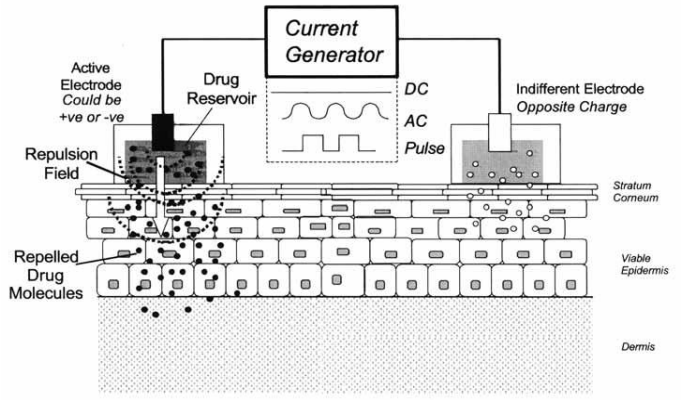


**Fig. 3:** The basic design of ionotphoretic delivery devices. Drug is placed on the skin under the active electrode, with the indifferent electrode positioned elsewhere on the body, and a current (<0.5mA) passed between the two electrodes effectively repelling drug away from the active electrode and into the skin (Roberts MS et al.,1997).

The Nernst-Planck equation has been used with modifications to predict iontophoretic enhancement ratios (ratio of steady state flux in presence of electric potential and in absence of potential) as the original equation lacks a term for convective electroosmotic flow (Srinivasan et al.,1990). Srinivasan and Higuchi (1990) and Pikal and Shah (1990) studied the contributions of osmotic flow and incorporated this fact into several equations. The increased flux during iontophoresis would include (Singh et al., 1994):

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

$$J^{ionto} = J^{electric} + J^{passive} + J^{convective}$$

$J^{electric}$ is the flux due to electric current application;
$J^{passive}$ is the flux due to passive delivery through the skin; and
$J^{convective}$ is the flux due to convective transport due to electro osmosis.

## APPLICATION OF IONTOPHORESIS

### Topical delivery

The ability to control the delivery rates of drugs by changes in current makes iontophoresis an attractive technique to use. Yamashita et al. studied the efficacy of iontophoretic delivery of calcium for treating hydrofluoric acid-induced burns (Yamashita et al.,2001).

### Treatment of hyperhydrosis

Hyperhydrosis (also called hyperhidrosis) is a condition that most often results in excessive sweating in the hands and feet. Tap water iontophoresis is one of the most popular treatments used in this condition. The procedure uses a mild electrical current that is passed through tap water to temporarily shut off sweat glands. According to one hypothesis, iontophoresis may induce hyperkeratosis of the sweat pores and obstruct sweat flow and secretion (although no plugging of the pores has been found) (Hill et al.,1981). Other proposed mechanisms include impairment of the electrochemical gradient of sweat secretion and a biofeedback mechanism (Karakoc et al.,2002). Successful induction of hypohidrosis by tap-water iontophoresis requires the application of 15–20 mA to each palm or sole for 30 min per session for 10 consecutive days, followed by one or two maintenance sessions per week (Hill et al.,1981).

### Diagnostic applications

Iontophoretic application of the drug pilocarpine produces intense sweating, allowing sufficient amounts of sweat to be collected and analyzed (Karakoc et al.,2002). This is now accepted as the primary test in the diagnosis of cystic f i b r o s is. (Table 5).

**Table 5:** Reverse iontophoresis in diagnostic applications

| Drug | Indication | References |
|---|---|---|
| **Phenytoin** | Ratio of extracted amount correlated well with subdermal concentration. | (Leboulanger et al.,2004) |
| **lithium** | Excellent correlation between subdermal lithium and iontophoretic extraction flux and iontophoresis tracked sudden changes in lithium concentration. | (Leboulanger et al.,2004) |
| **Caffeine, Theophyline** | Better extraction through stratum corneum than the stratum corneum stripped skin. | (Sekkat et al., 2002) |

### Ophthalmology

Iontophoresis has been used experimentally to deliver antibiotics into the eye." The principal disadvantage of this technique is the time required for direct contact of the electrode with the eye (Srinivasan et al., 1990).

### Otorhinolaryngology

Iontophoresis is a preferred method for obtaining anesthesia of the tympanic membrane prior to simple surgical procedures involving that structure. Iontophoresis of zinc has also been used for the treatment of patients with allergic rhinitis (Karakoc et al.,2002).

### Dentistry

Dentistry, probably to an even greater extent than physical therapy, has used iontophoresis. Beginning in the late 19th century, dentists applied local anesthetics to their patients prior to oral surgical procedures (Potts et al., 2002 and Pannatier et al.,1978). Gangarosa described the use of iontophoresis for three basic applications in dentistry: (1) treatment of hypersensitive dentin (eg, in teeth sensitive to air and cold liquids) using negatively charged fluoride ions; (2) treatment of oral ulcers ("canker sores") and herpes orolabialis lesions ("fever blisters") using negatively charged corticosteroids and antiviral drugs, respectively; and **(3)** the application of local anesthetics to produce profound topical anesthesia,as is done in some physical therapy applications (Potts et al., 2002).

### Non-invasive monitoring of glucose

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 Watchw Biographer (Cygnus Inc., Redwood City, CA, USA) (Potts et al., 2002). This device allows noninvasive extraction glucose across the skin, allowing a diabetic's glycemia to be evaluated every 10 min over several hours.

**Peptide delivery**

This is the most promising applications of iontophoretic transdermal delivery. Transdermal delivery itself offers the advantages of bypassing first pass metabolism and gastrointestinal degradation as well as patient compliance over the existing oral and parenteral routes of administration for peptide delivery. An additional advantage that it offers specifically for proteins and peptides is the avoidance of strong proteolytic conditions as found in the gastrointestinal tract (Pannatier et al.,1978). The delivery of oligopeptide, vasopressin, with transdermal periodic iontotherapeutic system (TPIS) (Chien.,1991).

**Table 6:** Iontophoresis and electroporation combination

| Drug | Indication | References |
|---|---|---|
| Tacrine Hydrochloride | Iontophoresis with electroporation and stripped skin produced greatest flux compared to each technique alone. | (Hirsch et al., 2005) |
| Buprenorphinc | Increased permeation of the drug from its solution by a factor of 14.27 compared to passive diffusion with shortened lag time and rapid onset. | (Fang et al., 2002) |
| Salmon calcitonin (SCT) & PTH combination | EP enhanced IP induced drug permeation by 17 fold in PTH and 3.5 fold in SCT. | (Chang et al., 2000) |

## VARIOUS SYNERGISTIC APPROACHES WITH IONTOPHORESIS

**Iontophoresis in conjunction with electroporation**

Iontophoresis and electroporation are both methods of electrically assisted transdermal drug delivery. Iontophoresis is more commonly used to deliver lipophilic small molecular weight drugs, while electroporation seems more effective for the delivery of some macromolecules such as antisense oligonucleotides, peptides and proteins. Drug delivery with iontophoresis and electroporation are thought to utilize different penetration pathways (Fig. 4). (Table 6)

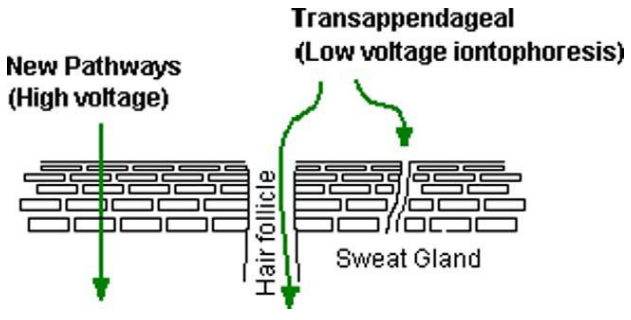


**Fig. 4:** Drug penetration pathway in low voltage iontophoresis and high voltage electroporation (Regnier et al.,1998)

Fluorescent microscopy and laser scanning confocal microscopy were used to visualize the FITC labeled phosphorothioate oligonucleotides transport at the tissue and cell level respectively in hairless rat skin after iontophoresis or electroporation (Regnier et al.,1998). In the SC the transportation pathways for FITC labeled phosphorothioate oligonucleotides were more transcellular during electroporation and paracellular during iontophoresis .The practical application of combining electroporation with iontophoresis is still in its initial feasibility stage much like the commercial development of electroporation devices for transdermal delivery of drugs.

**Table 7:** Iontophoresis & chemical enhancer combination

| Drug | Indication | References |
|---|---|---|
| Acetaminophen (non-ionic), buspirone (cationic), ibuprofen (anionic) | Lauric acid was found to enhance ibuprofen (anionic) flux. | (Sebastiani et al., 2005) |
| Insulin | DMA, EtAC and EtOH having skin barrier altering potential produced synergism with iontophoresis. | (Pillai et al., 2004) |
| Thiocolchicoside | Enhanced flux of the drug by a factor of 200 and 300 with 2 % and 4 % of lauric acid respectively was observed. | (Yamashita et al.,2001) |
| Buspirone Hydrochloride | Iontophoresis with Enhancers caused a synergistic effect over each technique alone. | (Meidan et al., 2003) |
| Insulin | Synergistic enhancement obtained which was dependent on the type and concentration of terpenes. | (Pillai et al., 2003) |
| Insulin | Synergistic effect on skin permeation of the drug but increased skin irritation. | (Pillai et al., 2003) |
| R- Apomorphine | Lauric acid- increased passive transport but affected iontophoretic transport slightly. DTAB- Inhibited both type of transport. Laureth-3-oxyetylene ether- Increased iontophoretic transport 2-3 fold (most effective). | (Li et al., 2002) |
| LHRH | 30 fold increase in flux was seen when combination was used as compared to passive alone. | (Smyth et al., 2002) |
| Timolol Maleate (TM) | The required transport rate achieved with low drug concentration and AUC was comparable to intravenous TM (30 µg/Kg). Azone® pretreatment eliminated the lag time and prolonged the duration of action of iontophoresis. | (Kanikkannan et al., 2000) |

**Iontophoresis in conjunction with chemical enhancers**

Although the use of iontophoresis results in much higher drug delivery if compared with conventional passive transdermal delivery, it still has limitations as a technique. Chemical enhancers can be used in combination with iontophoresis to achieve even higher drug penetration. In addition to increasing transdermal transport, a combination of chemical enhancers and electrically assisted delivery should also reduce the side effects such as irritation caused by high concentration of enhancers or stronger electric forces. The combined effects of enhancers and electrically assisted delivery depend on the physico-chemical properties of the

**Table 8:** List of drugs investigated recently for iontophoretic delivery

| Drug | Indication | References |
|---|---|---|
| Thiocolchicoside | Enhanced flux of the drug over passive control. | (Yamashita et al.,2001) |
| Rotigotine | Flux increased with drug concentration. With co-ions viz.TEA, flux of rotigotine increased while TBA showed no effect on flux. | (Nugroho et al., 2004) |
| Leuprolide (LHRH agonist) | Iontophoretic permeation was found to be double at pH-7.2 than at pH-4.5 (increased transference number was observed). | (Kochhar et al., 2004) |
| 5-Amino Levulinic acid (Ala) & its methyl ester (m-Ala). | Ala - steady state - 10-12 h. Flux- 65 nmole/cm2 . m-Ala -steady state - 2.5-4.0 h flux- 145 nmole/cm2. | (Merclin et al.,2004) |
| Gentamycin | Concentration achieved in cornea and aqueous humour was 12-15 times higher than the topical eye drop. | (Esther et al., 2004) |
| Salbutamol | Enhanced flux from the vehicle. | (Nolan et al., 2003) |
| Dextran sulphate | Cumulative amount fluxed from cathode was approximately 300 times more over passive and from anode it was 15 times more. | (Badkar et al., 2002) |
| Timolol maleate (TM) | Iontophoretic transport highest in human skin and lowest in rabbits. | (Kanikannan et al., 2001) |
| Diclofenac | Full plasma concentration achieved in 1 h. Drug delivery was proportional to current (371± 141 µgm / lt at 0.5 mA/cm$^2$ and 132 ± 62 µ gm/ lt at 0.2 mA/ cm2 ). | (Hui, et al., 2001) |
| Atenolol hydrochloride | Delivery of atenolol hydrochloride increased with increase in donor concentration. | (Jacobsen , 2001) |
| Buprenorphine | 8 fold increase in delivery by anode than cathode. | (Bose et al., 2001) |
| Piroxicam | 10 fold increased permeation. | (Curdy et al., 2001) |

penetrant, enhancer and their behavior under the influence of an electric field. Occasionally, the use of chemical enhancers was reported to result in reduced flux compared with using iontophoresis alone (Choi et al.,1999 and Chesnoy et al., 1999). However, more often synergistic effects have been reported such as those with fatty acids, and terpenes and others.(Table 7)

**Iontophoresis conjunction with sonophoresis**

Synergy between low-frequency ultrasound and iontophoresis would be expected since the techniques both enhance transdermal transport although through different mechanisms (Mitragotri et al., 2004). As a matter of fact, the disruption of SC lipid bilayer by the application of ultrasound can be utilized by further use of iontophoresis to increase transdermal drug transport to a greater degree. This combination has been found to enhance transdermal transport better than any of the single treatments alone. Iontophoresis combined with low frequency ultrasound was used in the transdermal delivery of sodium nonivamide acetate (SNA) (JY Fang et al.,2002). Pretreatment of the skin with low frequency ultrasound (0.2 W/cm2, 2 h) alone did not increase the skin permeation of SNA. The combination of iontophoresis (0.5 mA/cm2) and sonophoresis increased transdermal SNA transport more than iontophoresis alone.

**Iontophoresis in conjunction with microneedles**

Few studies have reported the combination of iontophoresis with microneedle technologies. This combination may provide the possibility of macromolecule transdermal delivery with precise electronic control. Lin et al. designed a Macrofluxw® and iontophoresis combined transdermal ISIS 2302 (Lin et al., 2001). The Macrofluxw® array, 2 cm$^2$, had a microprojection density of 240/cm2 and a needle length of 430 µm. Macrofluxw® and iontophoresis combined system was made by assembling the Macrofluxw array, a drug reservoir, a membrane, a conductive gel and the iontophoretic electrode.

**Table 9:** Studies done using pulsed iontophoresis

| Drug | Indication | References |
|---|---|---|
| LHRH and Nafereline | Higher flux obtained for pulsed waveform compared to constant DC. | (Johanna et al., 2004) |
| Ketorolac | Flux reduced when pulsed current was used. | (Tiwari et al., 2003) |
| Phthalic acid (PA), benzoic acid (BA), Verapamil (VR). | For PA, BA and VR, the cumulative permeated amount was higher at short pulses. | (Ishikawa et al., 2002) |
| Glibenclamide | Solution of pH-8.5 gave higher absorption rate than other two buffers. | (Takahashi et al., 2001) |
| Human Para thyroid hormone | Increase in HPTH hormone in all animals, creating a pulsatile pattern without the need of frequent drug administrations. | (Suzuki et al., 2001) |

**Iontophoresis in conjunction with ion-exchange materials**

For this combined technique, experimentally the ion exchange materials were initially immersed into drug solution for 3 h to overnight. Afterward, such a drug-loaded device (e.g. disc, a bundle of ion exchange fibers or hydrogel filled with ion exchange resins) was transferred to the donor part of a diffusion cell for in

vitro or in vivo tests (Jaskari et al., 2000, Kankkunen et al., 2002 and Kankkunen et al., 2002). The successful in vivo delivery of therapeutic dosage of tacrine, an anti-Alzheimer's disease agent, (Kankkunen et al., 2002).

**Table 10:** Iontophoretic products under different development stages (R. Panchagnula et al., 2000)

| Company | Device/system | Status |
|---|---|---|
| Dermion Inc. (Salt Lake City, Utah) | Wearable iontophoretic patches. | Under development |
| Janssen Pharmaceutica (Bererse, Belgium) | On-demand delivery system of fentanyl for acute pain management. | Phase III clinical trial |
| ALZA (Pala Alto, California; E-TRANS) | Electrotransport delivery of insulin. | Under development |
| Cygnus (Redwood City, California; Gluco Watch) | Glucose monitoring system based on reverse iontophoresis. | Awaiting US FDA approval |
| Becton Dickinson (Franklin Lakes, New Jersey) | Reusable power supply controllers<br>Lidocaine patches. | Under development<br>Phase III clinical trials |
| Iomed Inc. (Salt Lake City, Utah) | IontoDex-dexamethasone sodium phosphate system for acute local inflammatory conditions<br>Hydromorphone for pain management. | Phase III clinical trials<br>Phase IIb clinical trials |
| Elan Corporation (Westmeath, Ireland; Panoderm) | Disposable and reusable systems for delivery of anti-emetics and analgesics<br>Local delivery of antimicrobials to the skin. | Under development<br>Under development |

## CONCLUSIONS

It should be evident from this review that iontophoresis hold a lot of promise for the future of drug delivery. The use of iontophoresis to treat local conditions is well known (Sloan JB et al., 1986). Iontophoresis may also be useful for targeting deeper underlying tissues e.g. muscle in conditions such as osteoarthritis. musculoskeletal spasms and other local inflammations associated with sports injuries or accidents. More recently, iontophoresis is being oppressed for the controlled delivery of drugs for systemic indications. It is believed to be practical alternative to parenteral therapy since comparable plasma levels may be obtained by two methods and the pain and discomfort associated with repeated injection therapy can be prevail over by iontophoresis. Iontophoresis may be particularly useful for the effective delivery of peptide and protein drugs since these compounds exist in a charged form at physiological pH. Using iontophoresis, transdermal delivery of insulin, thyrotropin-releasing hormone, leuprolide, gonadotropin- releasing hormone, arginine-vasopressin and some tripeptides has been demonstrated. Combination of iontophoresis with electroporation, chemical enhancers, sonophoresis, microneedle and ion exchange material may provide easier and more accurate delivery of macromolecules and poorly water soluble compounds. The combined use of iontophoresis and other techniques are likely to yield useful and interesting data which will intensify the efforts to more fully explore other techniques as a means of transdermal drug delivery. It seems that iontophoresis is close to commercialization while research investigations are intensifying in the combined area of use.

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