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# IONTOPHORETIC TRANSDERMAL DRUG DELIVERY

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**Keywords:**

Iontophoresis, permeation enhancer, flux, electric current, Transdermal Drug Delivery, non-invasive

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## ABSTRACT

The skin has been used as a port for systemic delivery of therapeutic agents since several decades. 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. Iontophoresis is a method of non-invasive transdermal drug delivery based on the transfer of charged molecules using a low intensity electric current. The payback of using iontophoretic technique includes improved systemic bioavailability ensuring 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 review describes the history of iontophoresis, mechanism of iontophoretic permeation enhancement, principles and factors affecting iontophoresis and its applications for various dermatological conditions.

## INTRODUCTION:[1,5,8]

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. Transdermal delivery of drug through the skin to the systemic circulation provides a convenient route of administration for variety of clinical indications. In the development of new transdermal drug delivery the object is to obtain controlled, predictable, and reproducible release of drug into the blood stream of patient. Transdermal device act as drug reservoir and controls the rate of drug transfer. The transdermal drug flux is controlled by the devices instead of the skin, since the drug release from the device can be controlled accurately than the permeability of the skin. Iontophoresis is the facilitated movement of ions across a membrane under the influence of externally applied small electrical potential difference (0.5mA/cm2 or less), is one of the most promising novel drug delivery systems, which have proved to enhance the skin penetration and the release rate of a number of drugs having poor absorption/permeation profile through the skin. Iontophoresis is gaining wide popularity in the area of pain relief as it provides a non-invasive means of systemic administration of minute amount of drugs.

## HISTORICAL BACKGROUND:[5,29]

A comprehensive historical review of electrotherapy until 1965, including iontophoresis, is provided by Licht; a more recent overview has been published by Chien and Banga. According to Chien and Banga, claims of medication transfer by electricity have been made as early as 1745. Not until 1879, however, did Munck truly demonstrate the ability to deliver ions, by delivering strychnine into a rabbit with an electric current. A few years later, in 1898, hlorton published a book in which he described an experiment in which he drove finely powdered graphite into his skin.

The first transdermal drug delivery system was introduced in the United States over 20 years ago. The technology generated tremendous excitement and interest amongst the major pharmaceutical companies in the 1980s and 90s. Until the early 20$^{th}$ century, current mediated 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. 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).

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.

**Table no 1: recent studies and applications of iontophoresis[5]**

| SCIENTIST | DRUG | INDICATION |
|---|---|---|
| Popkin et al. | Hyaluronidase | Scleroderma |
| Schwartz et al. | Hyaluronidase | Lymphoedema |
| Coyer | Citrate | Rheumatic arthritis |
| Stolman | Various | Hyperhydrosis |
| Albrecht | Vincristine | Trigeminal neuralgia |

**IONTOPHORESIS:[2,4,7,9]**

The stratum corneum is the principle barrier for absorption of drugs through the skin and restricts the permeation of hydrophilic, high molecular weight and charged compounds into the systemic circulation. However many therapeutically active drug molecules are hydrophilic and possess high molecular weights example, peptides. Iontophoresis is the process which involves increased transport of solute molecules into a tissue using an electric current.

In Iontophoresis (IP), this external source of energy is in the form of an applied direct electric current. Electrical energy assists the movement of ions across the stratum corneum according to basic electrical principles of "like charges repel each other and opposite charge attract." In day to day life, a solution of the drug pad or gel is placed on the skin. An active electrode is placed elsewhere on the body. A small electric current, usually less than 1 mA, is applied for a time period, usually 15 to 20 min. Drug travels through the tissue and is available for its local effect.

**PRINCIPLE OF IONTOPHORESIS:**[10,18]

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 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 cathodaliontophoresis 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. 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.

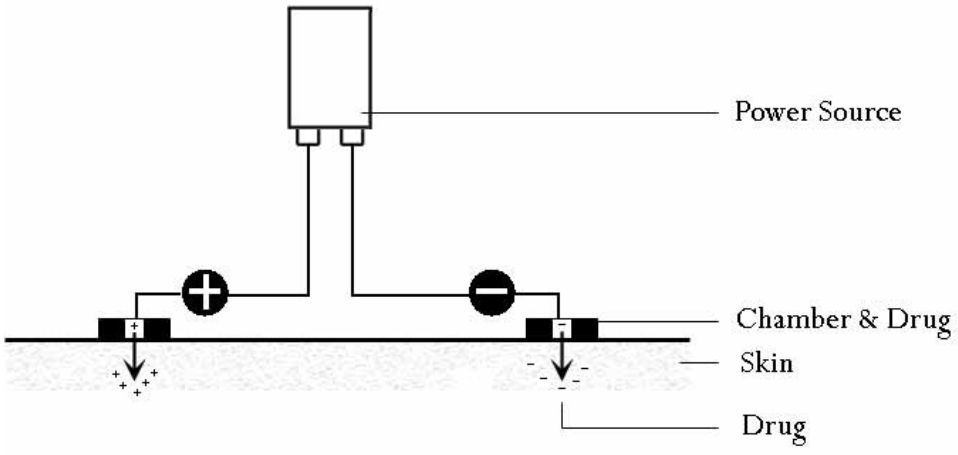


**Figure 1: Principle of Iontophoresis.**

**ADVANTAGES OF IONTOPHORETIC TECHNIQUE:[10]**

- Delivery of both ionized and unionized drugs.
- Permitting easier termination of drug delivery.
- Restoration of the skin barrier functions without producing severe skin irritation.
- Depending on the current applied it is enabling continuous or pulsatile delivery of drug.
- Improving the delivery of polar molecules as well as high molecular weights compounds.
- Ability to be used for systemic delivery or local (topical) delivery of drugs.

**MECHANISM:[1,11,8,15]**

In iontophoretic transport two mechanisms are involved. First one is Electromigration (also called as electrorepulsion) is the movement of ions across a membrane i.e. the skin under the direct influence of an electric current. Negatively charged drugs are therefore repelled into the skin under the cathode, whereas as the transfer of positively charged drugs occurs under the anode. The second mechanism is called electro-osmosis, which can be schematized as the volume flow induced by the current flow. As the isoelectric point (pI) of human skin is around 4-4.5, which is below its pH in physiological conditions, the skin will be charged negatively. Mechanism of Iontophoretic transport of drug across the skin involves diffusion, migration or electro-osmosis. The electrorepulsion effect gives the largest enhancement to the flux of small lipophilic cations. When the concentration of the ionic drug is very high, so that the drug carries most of the current, electro-osmotic flow has a very small effect on the drug flux.

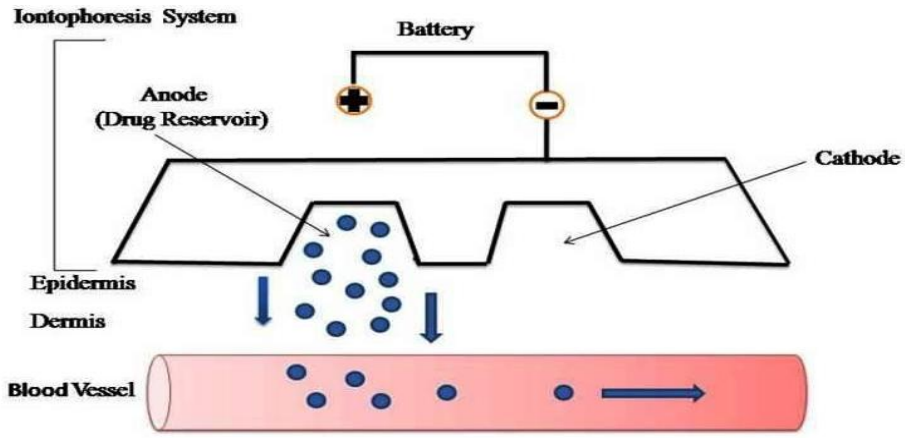


**Figure 2: Mechanism of Iontophoresis.**

**Table no 2 factors that are influence iontophoretic process:[25,26]**

| OPERATIONAL FACTORS | BIOLOGICAL FACTORS |
|---|---|
| 1. Composition of formulation: | 1. Intra and inter subject variability |
| Concentration of drug solution | 2. Regional blood flow |
| pH of donor solution | 3. Skin Ph |
| Ionic strength | 4. Condition of skin |
| Presence of co-ions | |
| 2. physicochemical properties: | |
| Molecular size | |
| Charge | |
| Polarity | |
| Molecular weight | |
| 3. Experimental conditions: | |
| Current density | |
| Current profile | |
| Duration of treatment | |
| Electrode material | |
| Polarity of electrodes | |

**OPERATIONAL FACTORS**

**Composition of formulation:**

Concentration of drug is one of the most important factors affecting iontophoretic process. An increase in concentration was shown to increase the apparent steady state flux of a number of drugs. E.g., AVP, metoprolol, butyrate, diclofenac sodium.

**pH:[1]**

This affects iontophoresis in two ways. The pH of the donor solution influences the pH of the skin and thus makes skin a permselective membrane especially if the pH of the skin raises above 4. This causes the carboxylic acid moieties in the skin to become ionized and the ca ionization of the drug itself. Thus a weakly basic drug will be ionized to a lower extent at pH higher than pKa and will not permeate by electromigration in presence of iontophoresis.

**Ionic strength and presence of other ions:**[12]

In iontophoresis the main aim is that the drug ion should carry maximum charge across the membrane. It follows that an increase in ionic strength will decrease drug delivery, as extraneous ions compete with the drug ions. 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 itself and can dominate the penetration into the skin thereby causing a decrease in transdermal flux of the drug. Many peptides widely studied for ionic strength showed a higher flux occurring at low electrolyte concentration. Similarly, drugs like ketorolac showed increased flux with decrease in ionic strength. A 50% reduction in benzoate flux occurred when an approximately equimolar amount of NaCl was added to donor compartment. Salicylic acid flux was found to decrease with the in- crease in concentration of HEPES buffer and 5-OH DPAT flux decreased with addition of NaCl. But occasionally an increase in ionic strength leads to an increased flux e.g., iontophoresis facilitated an increased skin permeation of AVP as the ionic strength of donor solution increased.

**PHYSICOCHEMICAL PROPERTIES:**

**Molecular size and molecular weight:**[1]

The molecular size of the solute is major factor governing its feasibility for drug delivery. Smaller and more hydrophilic ions are transported at faster rate than the larger ions, the permeability coefficients of solute across the skin are function of molecular size. When the molecular size increases, the permeability coefficient decreases.

**Charge:**[4]

Charge on molecules is an important physicochemical property governing iontophoretic transport; sign of the charge determines the mechanism. Increase in the charge will require pH to be decrease, which in turns directly decreases the electro-osmosis and electro transport process.

**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.

**EXPERIMENTAL CONDITIONS:**

**Current strength:[1,8]**

Current can easily be controlled by the use of electronics, it is a convenient mean to control delivery of drugs to the body. 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 nonspecific vascular reactions (vasodilatation) increased. In general, 0.5 mA/cm2 is often stated to be the maximum iontophoretic current which should be used on human beings.

**Current profile:**

Mostly, in the studies conducted on animals in vitro, current is kept constant and very low voltage of about 10 V is applied.

**BIOLOGICAL FACTORS:**

**Intra and inter subject variability:[5]**

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 and between hairy and hairless skin.

**Regional blood flow:[5]**

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 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.showed that the passive diffusion of hydrocortisone occurred maximally from the area with numerous hair follicle while lesser in area with thickest stratum corneum.

**APPLICATIONS OF IONTOPHORESIS:[5,8,9,10]**

**TREATMENT OF HYPERHIDROSIS:[27]**

It is the condition that often results in excessive sweating in the hand and feet. Tap water iontophoresis is most popular treatment used in the condition. According to one hypothesis, iontophoresis may induced hyperkeratosis of the sweat pores and obstruct sweat flow and secretion.

**TOPICAL DELIVERY:[9]**

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

**OPTHALMOLOGY:**

Iontophoresis is preferred to deliver antibiotics into the eye. The main disadvantage of this technique is the time required for direct contact of electrode with the eye.

**DERMATOLOGY:**

Iontophoresis has many uses in the field of dermatology. Except for the use of lidocaine for anaesthesia and the treatment of patients with hyperhidrosis, most uses of iontophoresis in dermatology have largely been abandoned. Iontophoresis with tap water or anticholinergic compounds has been used for the treatment of hyperhidrosis in palms, feet, and axillae.

**DIAGNOSTIC APPLICATION:**

Iontophoretic application of the drug pilocarpine produces intense sweating, allowing sufficient amounts of sweat to be controlled and analyzed. This is now accepted as the primary test in the diagnosis of cystic fibrosis.

**PEPTIDE DELIVERY:**

This is most promising application of iontophoresis. TDDs itself gives the advantages of bypassing first pass metabolism as well as patient compliances. An additional advantage that it offers specifically for proteins peptides is the avoidance of strong proteolytic as found in GI tract.

**Table no 3: iontophoretic products in market[8]**

| COMPANY | DEVICE/SYSTEM |
|---|---|
| Dermioninc. (salt lake city,) Com | Wearable Iontophoretic patches |
| Janssen Pharmaceutica (Belgium) | On demand delivery of fentanyl for pain management |
| ALZA (Pala alto, California) | Electrotransport delivery of insulin |
| Cygnus (redwood city, California) | Glucose monitoring system based on reverse Iontophoresis |
| Beeton Dickinson (Franklin lakes, new jersey) | Reusable power supply controllers Lidocaine patches |
| Elan corporation (Westmeath, Irelands; panoderm) | Disposable and reusable system for delivery of anti-emetics and analgesics |
| Iomedinc. (salt lake city) | IontoDex- dexamethasone sodium phosphate system for acute inflammation |

## CONCLUSION

Iontophoresis is a technique used to enhance the transdermal delivery of compounds through the skin via the application of a small electric current. The use of iontophoresis in medicine is likely to increase, because it offers a safe, convenient, non-invasive route of administration. 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 a transdermal drug delivery. Using iontophoresis, transdermal delivery of insulin, thyrotropin-releasing hormone, leuprolide, gonadotropin-releasing hormone, arginine-vasopressin and some tripeptides has been demonstrated. In addition, rapid progress in the fields of microelectronics, nanotechnology and miniaturisation of devices is leading the way to more sophisticated iontophoreric devices, allowing improved designs with better control of drug delivery.

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