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# IONTOPHORESIS-AN APPROACH FOR TRANSDERMAL DRUG DELIVERY

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**Abstract**

The goal of delivery system is to get optimal therapeutic management. But, it stillremains a challenge in the field of pharmaceuticals for delivery of ionic species and some nonionic. Several transdermal approaches have been used and recently there has been a great attentionin 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 beeliminated. 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 innovativefocus for research in drug delivery, with around 40% of the drug candidate being under clinical evaluation related to transdermal or dermal systems. The skin has been investigated for several decades as a route of drug administration and so far many drug delivery techniques which utilize alternative forms of energy have been explored to facilitate permeation of drugs across the skin. Amongst these, 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 [1-4]. It is a localized, non-invasive, convenient and rapid method of delivering water soluble, ionized medication into the skin. Iontophoresis provides the usual advantages of a trandermal route like, therapeutic efficacy improvement by bypassing hepatic "first pass" metabolism, avoidance of inconvenience caused by parenteral drug delivery and prevention of variation in the absorption seen with oral administration. Besides this, it also reduces the chance of dosing variation by providing programmed delivery of the drug. Iontophoresis also provides atherapeutic regimen leading to better patient compliance. It permits the use of a drug with a short biological half life since the drug is delivered to the target area without the need to recirculate in the blood. Moreover, the drug is delivered into the bloodstream directly without any delay. It also provides a rapid termination of the effect by turning off the iontophoretic delivery system. Thus, because of many advantage associated with this system, it has been an area of growing interest in the local and the systemic delivery of drugs.

**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 systemiccirculation. However, many therapeutically active drug molecules are hydrophilic and possess high molecular weights for example, peptides. 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. 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.

- Delivery of both ionized and unionized drugs.
- Depending on the current applied it is enabling continuousor 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 variabilityin view of the fact that the rate of drug delivery is moredependent 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, 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 aFranz diffusion cell to enhance the flux of an anion, it is termedcathodal 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.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 electro neutrality. Thus the movement of ions under physiological conditions is from the anode to the cathode. For loss of each cation (sodiumion in this case) from the electrode in this process, a counter ion, i.e. an anion, Cl −moves in the opposite direction from the cathodeto the anode. It is the transport number of each ion, which describes the fraction of the total current transferred by the ion anddepends 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 pores welling at the cathode.

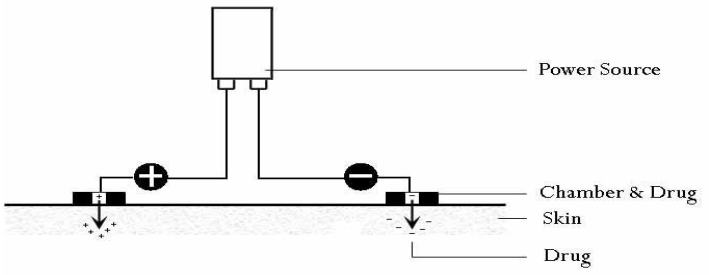


**Fig. 1:** Principle of Iontophoresis

**Merits:**

1. It is a non-invasive technique could serve as a substitute for chemical enhancers.
2. It eliminates problems like toxicity problem, adverse reaction formulation problems associated with presence of chemical enhancers in pharmaceuticals.
3. It may permit lower quantities of drug compared to use in TDDS, this may lead to fewer side effects.
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.
5. Iontophoresis prevent variation in the absorption of TDDS.
6. Eliminate the chance of over or under dosing by continuous delivery of drug programmed at the required therapeutic rate.
7. Provide simplified therapeutic regimen, leading to better compliance.
8. Permit a rapid termination of the modification, if needed, by simply by stopping drug input from the iontophoretic delivery system.
9. It is important in systemic delivery of peptide/protein based pharmaceuticals, which are very potent, extremely short acting and often require delivery in a circadian pattern to simulate physiological rhythm, eg. Thyrotropin releasinghormone, somatotropine, tissue plasminogen activates,interferons, enkaphaline, etc.
10. Provide predictable and extended duration of action.
11. Reduce frequency of dosage.
12. Self-administration is possible.
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.
14. An iontophoretic system also consists of a electronic control module which would allow for time varying of free-back controlled drug delivery.
15. Iontophoresis turned over control of local anesthesia delivery in reducing the pain of needle insertion for local anesthesia.

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.

17**.** Iontophoretic delivery prevents contamination of drugs reservoir for extended period of time.

**Demerits:**

1. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.

2. An excessive current density usually results in pain.

3. Burns are caused by electrolyte changes within the tissues.

4. The safe current density varies with the size of electrodes.

5. The high current density and time of application would generate extreme pH, resulting in a chemical burn.

6. This change in pH may cause the sweat duct plugging perhapsprecipitate protein in the ducts, themselves or cosmetically hyperhydrate the tissue surrounding the ducts.

7. Electric shocks may cause by high current density at the skin surface.

8. Possibility of cardiac arrest due to excessive current passing through heart.

9. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.

10. High molecular weight 8000-12000 results in a very uncertainrate of delivery.

**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 More formally, transdermal iontophoresis should be called electrically assisted transdermal delivery. The two principal mechanisms by which iontophoresis enhancesmolecular transport across the skin are:

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

(b) Electroosmosis, the convective movement of solvent that occurs through a charged "pore" in response to thepreferential passage of counter-ions when the electric field is applied. 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. 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. Mechanism of iontophoretic transport of drugs across the skin involves 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.

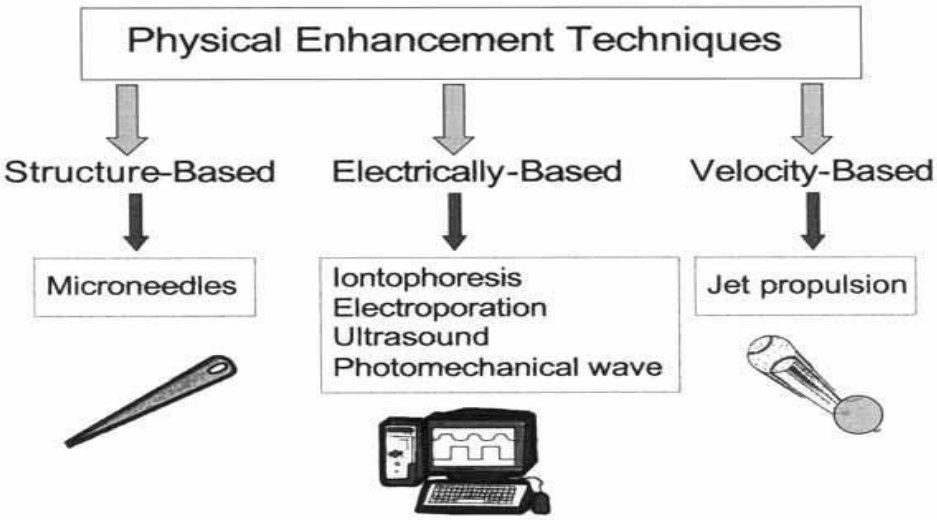


**Fig. 2:** Classification of the types of physical delivery technologies available for transdermal drug application.

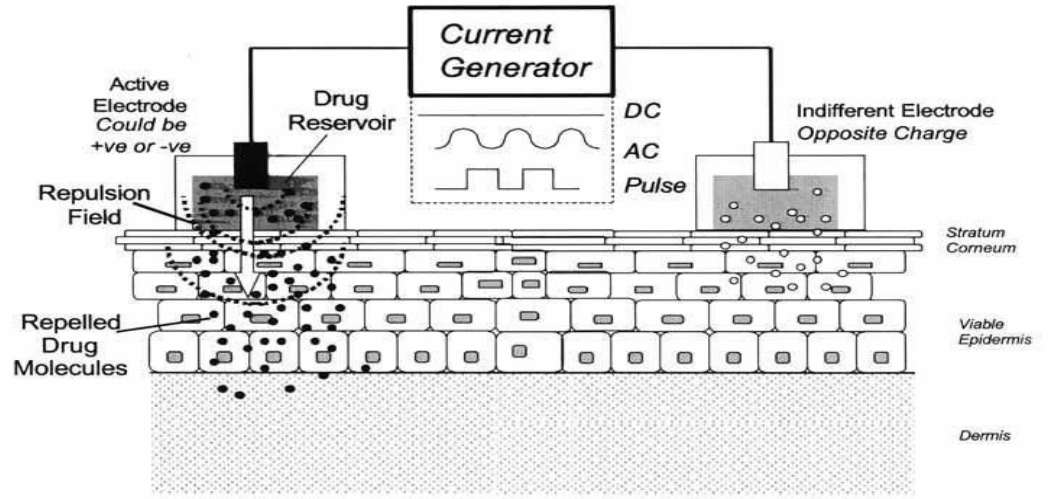


**Fig. 3:** The basic design of ionotphoretic delivery devices. Drug is placed on the skin under the active electrode, with the indifferent electrode positioned elsewhere on the body, and a current (<0.5mA) passed between the two electrodes effectively repelling drug away from the active electrode and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

**Application of Iontophoresis**

**Topical delivery**

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.

**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 thatis 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). Other proposed mechanisms include impairment of the electrochemical gradient of sweat secretion and a biofeedback mechanism. Successful induction of hypohidrosis by tap-water iontophoresis requires the application of15–20 mA to each palm or sole for 30 min per session for 10consecutive days, followed by one or two maintenance sessions per week.

**Diagnostic applications**

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

**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.

**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.

**Dentistry**

Dentistry, probably to an even greater extent than physicaltherapy, has used iontophoresis. Beginning in the late 19th century, dentists applied local anesthetics to their patients prior to oralsurgical procedures 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 chargedfluoride ions; (2) treatment of oral ulcers ("canker sores") andherpes orolabial is 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.

| Operational Factors | Biological Factors |
|---|---|
| **I. Composition of formulation**:<br>Concentration of drug solution<br>pH of donor solution<br>Ionic strength<br>Presence of co-ions<br>**II. Physicochemical properties of the permeant**:<br>Molecular size<br>Charge<br>Polarity<br>Molecular weight<br>**III. Experimental conditions:**<br>Current density<br>Current profile<br>Duration of treatment<br>Electrode material<br>Polarity of electrodes | I. Intra and inter subject variability<br>II. Regional blood flow<br>III. Skin pH<br>IV. Condition of skin |

**Table-1: Factors Affecting Iontophoretic Delivery of the Drug**

**Conclusion:**

It should be evident from this review that iontophores is hold a lot of promise for the future of drug delivery. The use of iontophoresis to treat local conditions is well known. Iontophoresis may also be useful for targeting deeperunderlying 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 parenteraltherapy 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 acharged form at physiological pH. Using iontophoresis, transdermal delivery of insulin, thyrotropin-releasing hormone,leuprolide, gonadotropin- releasing hormone, arginine-vasopressinand some tripeptides has been demonstrated. Combination of iontophoresis with electroporation, chemical enhancers, sonophoresis, microneedle and ion exchange material may provideeasier 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 datawhich 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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