The use of electric current – Iontophoresis for transcutaneous drug delivery – Novel drug delivery system (NDDS)

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ABSTRACT
The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is delivered, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to the targets in tissues with new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio recognition, and efficacy of drugs. These new strategies often called drug delivery system (DDS) are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bio conjugate chemistry, and molecular biology and have generated much attention during the last decades. Drugs administered through these systems escape first-pas metabolism and maintain a steady state scenario similar to a continuous intravenous infusion for up to several days. However, the excellent impervious nature of the skin offers the greatest challenge for successful delivery of drug molecules by utilizing the concepts of iontophoresis. The rationale behind using these techniques is to reversibly alter the barrier properties of skin, which could possibly improve the penetration of drugs to increase the systemic delivery with controlled input kinetics and minimum inter-subject variability.

Keywords: Pharmacokinetics, Pharmacodynamics, Immunogenicity, Bio recognition, Iontophoresis.

INTRODUCTION
The design of a dosage form, whether in the form of a tablet, capsule, pill, cream, liquid, ointment, aerosol, injectables, suppositories or patch, to deliver the exact amount of medicine at right time to the specific target becomes complicated if each medication were not to be delivered in an optional and preferred manner to the individual patient1. Newer dosage forms and drug delivery systems providing excellent improvement in drug therapy are
termed novel drug delivery system (NDDS) because of recent development with satisfactory results in the field of drug delivery. The NDDS are being investigated so as to alter the body distribution of drug(s) with a view to reduce the toxicity of drug and/or deliver them more efficiently to their site of action to improve therapeutic index and lower the toxicological risks from the dosage of drug. The increased attention on patients compliance and reduction in dose frequency has led to the development of an alternative and desirable approach of taking medicine, other than oral route for drug action, which is to deliver them through the skin – a major barrier to the delivery of transcutaneous drugs and pharmaceutical companies are continually involved in research to try to find new ways to enhance the delivery of topical drugs. Some of the novel advanced transdermal technologies include:

In recent times, there has been a growing interest in simulating the advantages of intravenous drug infusion by using intact skin as the port of drug administration. Skin is one of the most extensive and readily accessible organs of the human body. In modern day pharmaceutical practice, therapeutic compounds are applied to the skin for dermatological (within the skin), local (regional) and transdermal (systemic) delivery. For transdermal delivery of drugs, stratum corneum is the main barrier layer for permeation of drug which is the uppermost layer of the epidermis with a thickness of between 10-100 μm and consists of several layers of corneocytes (nucleate keratin filled cells) in laid in a lipid matrix, a continuous medium through the SC, arranged in bilayers. So to circumvent the stratum corneum and to increase the flux through skin membrane, different approaches for enhancement of penetration are used. Much effort has been dedicated to improving impermeability and one of the ways for circumventing the stratum corneum barrier include iontophoresis.

**Iontophoresis**

Iontophoresis, derived from the Greek “ionto” meaning ‘ion’ and “phoresis” meaning ‘to bear’ involves enhancing the permeation of a topically applied therapeutic agent by the application of a low level electric current either directly to the skin or indirectly via the dosage form.
Historical Background of Iontophoretic Process
Clinical application of current can be traced back to the ancient time of the golden age of the Greek civilization and was probably originated by Varatti in 1747. Galvani and Votta in 18th century combined the knowledge that the electricity can move different metal ions and the movement of the ions produce electricity. This method of administering pharmacological agents by iontophoresis became popular at the beginning of 20th century due to work of Leduc (1900) who introduced the term iontopherty and formulated the laws for this process. Until the early 20th century, current medicated drug delivery was known as “cataphories”. Frankenhaues is said to have introduced the term “iontophoresis” before 1908. The phoresor device was the first iontophoretic system to be approved by the FDA in the late 1970’s as a physical medicine therapeutic device in order to enhance patient’s compliance, the use of patient-friendly, portable and efficient iontophoretic systems have been under intensive development over the years. Such improved systems include the Vyteris and E-TRANS iontophoretic devices.

Iontophoretic Research and Drug Delivery
The physiochemical properties of the molecule have an effect on the contribution of the follicular and non-follicular routes of penetration. Hydrophilic molecules tend to localize in the hair follicles, whereas lipophilic molecules are mostly distributed in the lipid intercellular organs of the SC and the lipid membrane of the epidermal keratinocytes. Since passive transdermal permeation of the majority of the drugs needs enhancement to achieve clinically relevant plasma concentration, both chemical and physical enhancement methods have been developed. Iontophoresis is one of the physical methods. There are three major enhancing mechanisms for drug reflux through the skin, which include; Iontophoresis (also known as electro repulsion, electro migration or Nernest-Planck effect), electro-osmotic flow and current induced increase in skin permeation, also known as damage effect. Electro repulsion is the direct effect of the applied electric field on a charged permeant and gives the largest enhancement to the flux of small lipophilic cations. The second mechanism, electro osmosis, results from the fact that the skin supports a net negative charge at physiological pH, the counter ions are cations and the electro osmotic flow is thus from anode to cathode. Therefore, the cathodic delivery of anions is hindered and the anodic delivery of cations is assisted by electro osmosis which has a positive contribution to the transport of cations and a negative contribution to the transport of anions under normal physiological conditions. The impact of electro osmosis ion transfer increases with the size of the ion. The contribution of electro osmosis can be so significant that the delivery of large anion from the anodic compartment can be more efficient than delivery from cathode, this is called wrong way iontophoresis. The other mechanism is current induced increase in skin permeation, also known as damage effect. In the presence of an electric field, electro migration and electro osmosis are the dominant forces in mass transport.

Diagram of iontophoretic technique: as current is applied the drug cations are repelled and move through the skin and eventually they are absorbed in the systemic circulation.
Because of the complex nature of iontophoretic delivery, a number of attempts have been made to define the rate of iontophoretic delivery. Abramson and Gorin derived an equation to compare the iontophoresis flow to electric mobility, electroosmosis and simple diffusion. The increased flux during iontophoresis includes:

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

\[ J_{\text{ionto}} = J_{\text{electric}} + J_{\text{passive}} + J_{\text{connective}} \]

\[ J_{\text{electric}} = \text{The flux due to electric current application.} \]

\[ J_{\text{passive}} = \text{The flux due to passive delivery through the skin.} \]

\[ J_{\text{connective}} = \text{The flux due to connective transport due to electro Osmosis.} \]

**Factors Affecting Iontophoretic Delivery System**

Many factors including the physiochemical properties of the compound, drug formulation, equipment used, biological factors, skin temperature and duration of iontophoresis effect the transport and can be divided into operational and biological factors. The following factors have to be considered:

1) **Influence of pH:** For optimum iontophoresis, it is desired to have a relatively large proportion of the drug in ionized state. However, this must be counterbalanced with delivery of a drug at a pH that is tolerable and safe for the patient.38

2) **Current strength:** The current is usually limited to 1 mA due to patients comfort considerations and should not be applied for more than 3 min because of local skin irritation and burns.39,40

3) **Ionic competition:** The use of buffering agents as co-ions (anion of equal charge but of different type is referred as co-ion) which are usually smaller and more mobile than the ion to be delivered results in reduction of number of drug ions to be delivered through the tissue barrier by applied current, that is when a positively charged drug is diluted in saline, the sodium ions will compete with the amount of drug ions to be delivered. Ideally the use of buffer system should be avoided, but if this is not possible, alternative buffers consisting of ions with low mobility or conductivity are preferred.41

4) **Drug concentration:** Depending on the drug used, the steady-state flux (ion movement) has been shown to increase with increasing concentration of the solute in the donor compartment, i.e, in the delivery electrode. Increased uptake by the skin during and after IP with an increase in drug concentration has been reported.42,43

5) **Molecular size:** In general when the molecular size increases, the permeability coefficient decreases. However, there are certain solutes
with a relatively high molecular size (eg insulin, vasopressin and several growth hormones), which have also been shown to penetrate the skin barrier into the systemic circulation.  

6) **Drug salt form:** It has been reported that different salt forms have different specific conductivities and that conductivity experiments in vitro will provide information concerning the general solubility of a drug and must be considered along with the pH of the solution for determining the amount of drug in the ionized state.

7) **Biological factors:** Patient anatomical factors that influence the depth of penetration that is variable from patient to patient include skin thickness at the site of application, presence of subcutaneous adipose tissue and size of other structures including skeletal muscle. Additionally, the presence and severity of inflammation can influence drug penetration due to the increased temperature.

### Selection Criteria For Drug Candidate

Transdermal route of drug administration has certain inherent difficulties that make it unsuitable for a large number of drugs and an ideal characteristic drug should be possess following criteria:

- A TDDS should not cover an area more than 50 cm² and daily dose should be of order of few mg, the effective concentration of drug should be low, presumably in the ng/ml, the active ingredients should not cause any skin toxicity or irritation, the drug should preferably be on low molecular weight as diffusion is dependent on molecular size, the drug should have a low melting point so that it acts on normal body temperature, drugs, which degrade in the GI tract or are inactivated by hepatic first pass effect, should have adequate hydrophilic and lipophilic balance to negotiate the lipid barrier of stratum corneum before being partitioned into the aqueous viable tissue and the half life of the drug should be short.

There is a wide variety of drugs that has been investigated is reported recently for iontophoretic delivery and include delivery of anaesthetics (eg lidocaine), steroids and retinoids to treat acne scarring, for the relief of palmar and plantar hyperhidrosis, pilocarpine in diagnosis of cystic fibrosis, ketoprofen in subcutaneous tissues and joints, fentanyl, arginine and vasopressin (AVP), atenolol, buprenorphine, leuprolide, piroxicam, rotigotine, salbutamol, thiocolchicoside and timolol maleate.

### Merits and demerits of transdermal iontophoretic system

#### Merits

It is a non-invasive technique that could serve as substitute for chemical enhancer, eliminates problems like toxicity problems, adverse reaction, formulation problems associated with presence of chemical enhancers in pharmaceuticals, permits lower quantities of drug compared to use in TDDS, thereby decreasing side effects, eliminate the chance of over or under dosing by continuous delivery of drug programmed at required therapeutic rate, permit a rapid termination of the modification, simply by stopping drug input from iontophoretic delivery system and self administration is possible.

#### Demerits

Arrangement to protect electric shock needed, an excessive current density usually results in pain, burns may be caused by electrolyte changes within the tissues, ionic form of drug in sufficient concentration is necessary for iontophoretic delivery and the treatment is somewhat costly.

### Clinical applications of iontophoresis in other disciplines

**Dentistry**

Iontophoresis has been used for treatment of hypersensitivity dentin (in teeth sensitive to air and cold liquids) using negatively charged fluoride ions, treatment of oral ulcers and herpes lesions using negatively charged corticosteroids and antiviral drugs, respectively.

**Dermatology**

Iontophoresis with lidocaine, tap water or anticholinergic compounds has been used for treatment of patients with hyperhidrosis of palms, feet and axillae.
CONCLUSION
Transdermal technology ensures as much as 95% of a supplement reaches the cells where it is needed. Doctors around the world are calling Transdermal delivery “The delivery system of the future” and found fantastic alternatives to pills and tablets. Considerations that are all important for design and development of pharmaceutical products intended for application into the skin require an ideal skin penetration enhancer, for which continual research has occurred over a number of decades. Although many potent enhancers have been discovered, their clinical application has been limited because of their toxic side effects. However, the recent approaches for penetration enhancement do not compromise skin barrier function as do chemical and physical penetration enhancement technique, and hence iontophoresis and phonophoresis can serve as better alternative. The iontophoretic delivery of macromolecules allows the strategy for non-invasive transdermal delivery of peptide-based pharmaceuticals, and contributes to further future advancement toward recombinant DNA technology. Although iontophoresis provides many benefits and seems to be more effective than other techniques, there is a need for further research and judicious use of technology with microelectronics devices which could prove it to be a ‘potential emergence to transdermal drug delivery’.

REFERENCES


