



IONTOPHORETIC DRUG DELIVERY: A NOVEL APPROACH THROUGH TRANSDERMAL ROUTE

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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 the Iontophoretic technique has been widely used. This technique of facilitated movement of ion across a membrane under the influence of an externally applied potential difference is one of the most promising physical penetrations enhancing method. The rationale behind using this technique is the capability of this method to increase the systemic delivery of high molecular weight compounds with controlled input kinetics. Also improved systemic bioavailability, ensuring from bypassing the first pass metabolism. This article presents a review of literature relating to iontophoresis. This review briefly describes the history of iontophoresis and discussion of factors which affect Iontophoretic drug delivery. Present review also provides its applications for various clinical conditions.

Key words: Iontophoresis, Flux, Transdermal Drug Delivery (TDDS).

INTRODUCTION

The transdermal route has become one of the most successful and innovative focus for research in drug delivery. 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 [1]. 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.

An increasing number of TDD products continue to deliver real therapeutic benefit to patient around the world. More than 35 TDD products have been approved by the FDA. Several transdermal approaches have been used and recently there has been a great attention in using Iontophoretic technique for the transdermal drug delivery of medication. The method of iontophoresis was described by pivati in 1747. Galvani and vota two scientist working in 18th century combined the knowledge that electricity

can move the different metal ions and vice versa [2]. The method of administering pharmacological agents by iontophoresis becomes popular at the beginning of 20th century. Due to the work of Leduc (1900), who introduce the term iontotherapy and formulated the laws for this process. Iontophoresis can define as the process in which the flux rate of absorption of ionic solutes into or through skin is enhanced by applying a voltage drop/electric field across the skin. Transdermal Iontophoretic technique is capable of administering drugs in a pulsatile pattern by alternately applying and terminating the current input at programmed rate.

Iontophoresis which is the facilitated movement of ions across a membrane under the influence of an externally applied small electric potential difference (0.5mA/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 number of drugs having poor absorption / permeation profile through skin [3].

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IONTOPHORESIS

The iontophoresis is the process which involves increased transport of solute molecules into a tissue using an electric current. The highly lipophilic nature of skin restricts the permeation of hydrophilic, high molecular weight and charged compounds through the stratum corneum into the systemic circulation [5]. However, many therapeutically active drug molecules are hydrophilic in nature and possess high molecular weights. This technique is capable of expanding the range of compounds that can be delivered transdermally [6].

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 in pad or gel is placed on the skin. An active electrode is placed on this pad or gel and the return electrode 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 [2]. The drug travels through the tissue and is available for its local effect [4].

PRINCIPLES OF IONTOPHORESIS

The Iontophoretic technique is based on the general principle that like charges repels each other and opposite charge attract. Thus during iontophoresis, if delivery of positively charged drug is desired, the charged drug is dissolved in the electrolyte surroundings the electrode of similar polarity, i.e. anode. An application of electromotive force the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body [2]. Communication between the electrodes along the surface of the skin has been shown to be negligible. When cathode is placed in the donor compartment of the Franz diffusion cell to enhance the flux of an anion, it is termed cathode iontophoresis and for anodal iontophoresis the situation would be reversed. If any neutral 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 cathode [4].

MERITS

- It is non-invasive technique could serve as substitute for chemical enhancers.
- Eliminate problems like toxicity, adverse reaction, and formulation related problem.
- It may permit lower quantity of drug compared to TDDS; this may lead to fewer side effects.
- Prevent variation in the absorption of TDDS.
- Eliminate chance of over and under dosing by continuous delivery of drug programmed at the required therapeutic rate.
- Provide simplified therapeutic regimen, leading to better compliances.
- Permit rapid termination of the modification.
- It is important in systemic delivery of peptide / protein based pharmaceuticals, which are highly potent.

- Provide predictable and extended duration of action.
- Reduced frequency of drug, self administration is possible.

DEMERITS

- Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.
- An excessive current density usually leads to pain.
- Burns are caused by electrolyte changes within the tissue.
- The safe current density varies with electrode size.
- The high current density and time of application would generate extreme pH, resulting in chemical burns. This change in pH causes the sweat duct plugging which leads to precipitation of protein in ducts.
- Electric shock may be caused by high current density at the skin surface.
- Possibility of cardiac arrest due to excessive current passing through heart.
- High molecular weight results in vary uncertain rate of delivery.

FACTORS AFFECTING IONTOPHORETIC DRUG DELIVERY OF THE DRUG

PHYSICO-CHEMICAL PROPERTIES

Molecular size and molecular weight

The molecular size of the solute is a major factor governing its feasibility for drug delivery. Smaller and more hydrophilic ions are transported at a faster rate than the larger ions, the permeability coefficients of solute across the skin are a function of molecular size. When the molecular size increases, the permeability coefficient decreases [1].

Charge

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 decreased, which in turn directly decreases the electroosmosis and electro transport process [4].

Concentration

Concentration of the drug is one of the most important factors. An increase in Concentration was shown to increase the apparent steady flux of the drug. The concentration dependent Iontophoretic delivery has not been fully investigated, some authors reported that as the concentration of drug, increase in the reservoir system then permeation of drug also increases.

DRUG FORMULATION RELATED FACTORS

pH

pH is an important factor governing the Iontophoretic delivery of the drug; this affects iontophoresis in two ways. The pH of the donor solution influences the pH of the skin and thus makes the skin a perm selective membrane especially if the pH of the skin

rises above 4. The pH of the donor solution also affects the ionization of the drug itself. Changes in the pH are also considered responsible for the discomfort and skin irritation associated with iontophoresis [1].

Ionic strength

The ionic strength of drug delivery system is proportional to the Iontophoretic permeation of drugs. Some authors reported that increasing the ionic strength leads to decreases the rate of permeation, and has no significant effect on penetration up to the 0.5

Presence of co-ions

An ion of equal charge but of different type is referred as co-ion. The buffering agents used to maintain pH of the donor medium is source of co-ions. These co-ions are generally more mobile and smaller in size than the drug ions. The presence of co-ions results in competition between the drug and co-ion, a reduction of the fraction of current carried by the drug and thus a reduction in the transdermal Iontophoretic flux of the drug [7].

EXPERIMENTAL FACTORS

Current strength

Current can easily be controlled by the use of electronics. Constant direct current has been used in Iontophoretic application, but we contend that constant current generator should be used to provide consistent current flow while the skin resistance is changing. There is linear relation between the observed fluxes of a 1cm^2 ; the current is limited up to 1mA due to patient comfort consideration [3]. This current should not apply for more than 3 min because of local skin irritation and burns. With increasing current, the risk of non specific vascular reactions increased. In general, $0.5\text{mA}/\text{cm}^2$ is often stated to be the maximum Iontophoretic current [1].

Current density

Current density is the quantity of current delivered per unit surface area. The current should be sufficiently high to provide desired delivery rate. It should not provide harmful effects to the skin. There should be quantitative relationship between the applied current. The drug should be electrochemically stable [5].

Pulsed current

The continuous use of direct current, proportional to time, can reduce the Iontophoretic flux because of its polarization effect on the skin. This can be overcome by the use of pulsed DC which is a direct current delivered in periodic manner. During off stage the skin gets depolarized and returns to the initial polarized state. However Burnett showed that enhanced skin depolarization can decrease the efficiency of drug transport if the frequency of pulsed current is very high [8].

Duration of application

The transport of drug delivery depends on the duration of current applied in Iontophoretic drug delivery.

The Iontophoretic penetration of the drug linearly increased with increasing application time [4].

Electrode material

The electrode materials used for Iontophoretic delivery are to be harmless to body and sufficiently flexible. The most common electrodes are aluminium foil, platinum and silver-silver chloride electrode used for IP. Electrode Ag/AgCl are the most preferred as they resist the change in pH which is generally seen during the use of platinum or Zn/ZnCl electrodes. The positioning of electrodes in reservoir depends on the charge of the active drug. The distribution of the drug within the skin depends on the size and position of electrodes. These are usually selected according to individual needs. Larger electrode areas introduce the greater amount of drug but lesser current density is tolerated to the skin [2].

MECHANISM

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

- Charged ion is repelled from an electrode of the same charge.
- Electroosmosis; the convective movement of solvent that occurs through a charged pore in response to applied electric field.

The mechanism of iontophoresis is based on the physical phenomenon that "like charges repel and opposite charges attract". 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.

Consider delivery of negatively charged drug across the biological membrane, it is placed between negative electrode (cathode) and skin [1]. The drug ion is then attracted through the skin towards the positive electrode by an electromotive force provided by the cell. Once the drug has passed through the outer barrier of the 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 [6].

Mechanism of Iontophoretic transport of drug 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 the voltage difference is applied across the charged. This flow involves motion of fluid without concentration gradient [1].

APPLICATIONS OF IONTOPHORESIS

Treatment of hyperhidrosis

It is a condition that most often results in excessive sweating in the hands and feet. Tap water iontophoresis is the most popular treatment used in this condition. According to

one hypothesis, iontophoresis may induced hyperkeratosis of the sweat pores and obstruct sweat flow and secretion.

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 condition as found in GI tract.

Non-invasive monitoring of glucose

Electro osmosis flow generated by application of low level current has been used for extraction of glucose through the skin. Reverse iontophoresis with in situ glucose sensors has been used in GLUCO WATCH BIOGRAPHER (Cygnus Inc.Redwood city,USA). This device allows non-invasive extraction glucose across the skin, allowing diabetics glycaemia to be evaluated every 10min.

Dentistry

In the beginning of the 19th century, dentist applied local anaesthetics prior to the oral surgical procedure. Gangarosa described the use of iontophoresis for three basic applications in dentistry: 1) Treatment of hypersensitive dentin using negatively charged fluoride ion. 2) Treatment of oral ulcers using negatively charged corticosteroids and antiviral drugs. 3) Application of local anaesthetics to produce profound topical anaesthesia.

Ophthalmology

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 [9-14].

Diagnostic applications

Iontophoretic application of the pilocarpine produce intense sweating, allowing sufficient amount of sweat to be collected and analyzed. This is now accepted as the primary test in the diagnosis of cystic fibrosis. Other drugs such as phenytoin, lithium, caffeine and theophylline are used for the diagnostic application [6].

NEW GENERATION APPROACH

Various other methods of penetration enhancers are used other than iontophoresis. That include ultrasound, chemical enhancer, electroporation, use of micro needles, ion exchange material have been used for enhancing transdermal drug transport. The combination of iontophoresis with these techniques has been used for the TDDS.

Iontophoresis with Chemical Enhancers

Chemical enhancers increase the transdermal drug delivery via several ways, which include increase drug solubility, increased drug partitioning into the stratum corneum and by the disruption of the intracellular protein.

Chemical enhancers can be used in combination with iontophoresis to achieve higher drug penetration. 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 use of chemical enhancer was reported that propylene glycol and oleic acid enhance transdermal transport of AZT in combination of iontophoresis [5].

Iontophoresis with Ultrasound/ Sonophoresis

Synergy between iontophoresis and ultrasound is predictable since the both technique enhance transdermal transport through different mechanism. Application of ultrasound should disorder the lipid bilayer of the skin by introducing new pathway. This disruption of lipid bilayer can be utilized by the further use of iontophoresis to increases drug transport to a greater degree. This combination has been found to enhance transdermal transport better than any of the single treatment used alone. Iontophoresis combined with sonophoresis was used in the transdermal delivery of sodium nonivamide acetate. Also the enhancement of heparin flux due to this combination was about 56 fold applied only for 1hr. This enhancement was higher than the sum of those obtained during ultrasound alone and iontophoresis alone [15-18].

Iontophoresis with Electroporation

Electroporation may create new transport pathways in the stratum corneum, thus assist the passage of current during iontophoresis. Electroporation seems more effective for the delivery of some macromolecules such as oligonucleotides, peptides and protein. The mechanism of drug transport is similar to that with sonophoresis. Chang *et al.* studied the effect of iontophoresis and electroporation on transdermal delivery of salmon calcitonin and parathyroid hormone through human epidermis. Author state that a combination of electroporation and iontophoresis induced higher transdermal permeation, than either one technique alone. Electroporation also shortened the lag time of Iontophoretic transdermal delivery of salmon calcitonin [19].

Iontophoresis in Conjugation with Microneedles

Few studies have reported the combination of the iontophoresis with micro needles technologies, this combination may provide the possibility of macromolecule transdermal delivery with precise electronic control. Lin *et al.* designed a macroflux and iontophoresis combined transdermal ISIS2302 [20].

Iontophoresis with Ion-Exchange Materials

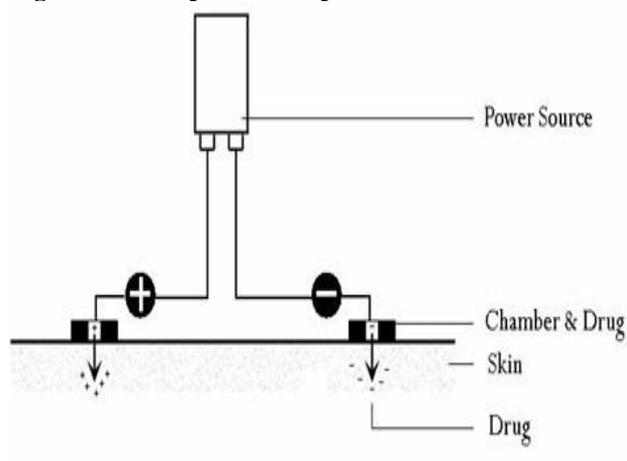
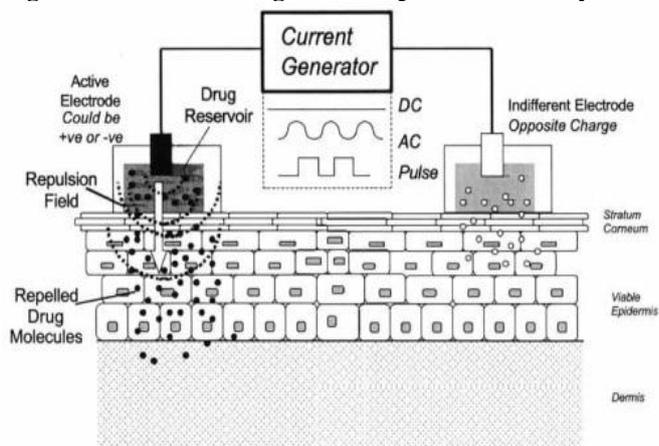
For this combined technique, experimentally the ion exchange materials were initially immersed into drug solution for 3hr to overnight. Such drug loaded device was transferred to the donor compartment of the diffusion cell for *in vitro* or *in vivo* test. The successful *in vivo* delivery of therapeutic dosage of tacrine was studied [21].

Table 1. Iontophoretic treatment between 1800 and 1900

Scientist	Year of reporting	Drugs used
Richardson	1858	Chloroform
Erb	1884	Various
Wagner	1886	Cocaine
Manzieri	1888	Atropine, quinine
Lauret	1885	Various
Corning	1886	Cocaine
Peterson	1889	Cocaine
McGraw	1888	Cocaine
Cagney	1889	Potassium iodide
Edison	1890	Lithium salt
Westlake	1892	Pyrazone, Cocaine
Morton	1898	Cocaine

Table 2. Iontophoretic Products in Market

Company	Device/system
Dermion inc.(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
Becton Dickinson(Franklin lakes, new jersey)	Reusable power supply controllers Lidocaine patches
Iomed inc. (salt lake city,)	OntoDex- dexamethasone sodium phosphate system for acute inflammation
Elan corporation (Westmeath , Irelands; panoderm)	Disposable and reusable system for delivery of anti-emetics and analgesics

Figure 1. Principle of Iontophoresis**Figure 2. The basic design of Iontophoretic delivery devices**

CONCLUSION

Iontophoresis is the process which involves increased transport of solute molecules into a tissue using small electric current has greater advantage over the transdermal drug delivery. The use of iontophoresis in medicine is likely to increase, because it offers a safe, convenient, non-invasive route of administration. It should be evident from this review that iontophoresis holds a lot of promises for the future of drug delivery. Iontophoresis also can be used for the targeting deeper

underlying tissue. It can be an alternative to the parental therapy since comparable plasma levels can be attained and pain and discomfort associated with injection can be overcome. Combination of iontophoresis with other techniques such as electroporation, chemical enhancers, sonophoresis etc may provide easier and more accurate delivery of peptides and poorly water-soluble drugs. It seems that iontophoresis is close to commercialization while research investigations will be more useful in the coming era.

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