



ISSN: 0975-766X
Review Article

Available Online through
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IONTOPHORESIS - AN ADVANCEMENT IN TRANSDERMAL DRUG DELIVERY SYSTEM

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Received on 16-08-2010

Accepted on 28-08-2010

ABSTRACT

The objective of transdermal delivery system is to achieve optimum therapeutic management. But, it still remains a challenge in the field of pharmaceuticals for delivery of ionic species such as proteins and peptides. Development of iontophoretic system is a breakthrough in this field designed to improve the delivery rate of ionic compounds. This technique generates an electrical potential gradient that facilitates the movement of solute ions across the membrane. Iontophoresis is the process of increasing the penetration of drugs into the skin by application of an electric current. The drug is applied under an electrode of the same charge as the drug, and a return electrode opposite in charge to the drug is placed at a neutral site on the body surface. Electrical energy assists the movement of ions across the skin using the principle "like charges repel each other and opposite charges attract". Iontophoresis seems to be an ideal candidate to sort out the limitations associated with the delivery of ionic drugs. In this review, efforts have been made to summarize all the aspects of iontophoretic delivery including history, mechanism, principles, types, various factors affecting the drug delivery and its application for various dermatological conditions.

Keywords: Iontophoresis, Transdermal Drug Delivery System, Stratum Corneum, Electro-osmosis

Introduction

The objective of transdermal delivery system is to achieve optimum therapeutic index, but delivery of ionic species such as proteins and peptides is still challenging. Development of iontophoretic system is a

breakthrough in this field which is designed to improve the delivery rate of ionic compounds. This technique generates an electrical potential gradient that facilitates the movement of solute ions across the membrane. Iontophoresis is the process of increasing the penetration of drugs into the skin by application of an electric current, the same and opposite charged electrode. Drug is placed at the neutral site on body surface. Electrical energy assists the movement of ions across the skin using the principle "like charges repel each other and opposite charges attract".

Definition of iontophoresis

"Iontophoresis is a process of transportation of ionic molecules into the tissues by passage of electric current through the electrolyte solution containing the ionic molecules using a suitable electrode polarity." This means it would involve an electromotive force. In the body, ions with a positive charge (+) are driven into the skin at the anode and those with negative charge (-) at the cathode.

Transdermal iontophoretic technique is capable of administering drugs in a pulsatile pattern by alternately applying and terminating the current input at programmed rate. In addition, delivery rate can be controlled by the intensity of applied electric current or Electro-chemical potential gradient.¹

Mode of administration can be passive or facilitated. In passive administration, the non-ionized drug traverses the skin through the stratum corneum. The skin, being a semi-permeable membrane, allows only a small amount of any drug molecule to passively penetrate the skin.¹⁰ Ionized drugs do not easily penetrate this barrier and are not suitable for routine trans-dermal delivery unless an external source of energy is provided to drive the drug across the skin. Facilitated diffusion can utilize either ultrasound (phonophoresis) or electrical (iontophoresis) energy. In iontophoresis, this external source of energy is in the form of an applied direct electrical current.²

Historical Development

The idea of applying electric current to increase the penetration of electrically charged drugs in to the surface tissue was probably originated by *Veratti* in 1747. In the latter part of 19th century, Morton conducted an experiment to introduce graphite iontophoretically into his arm. The first well documented experiment was done

in 20th century by *Leduc* in 1908. Placing two rabbits in series with a direct current generator, *Leduc* demonstrated the introduction of strychnine and cyanide ions in to rabbits when the correct polarity was applied. The results were rather dramatic. The first rabbit was seized by tetanic convulsions due to introduction of strychnine ions, while the second rabbit died with symptoms of cyanide poisoning.

Today, the treatment of hyperhidrosis is the most successful and popular application of iontophoresis in dermatologic medication (*Sloan & Soltani*, 1986). *Shelly et al.* (1950) showed that antihistaminic compounds may be administered percutaneously by iontophoresis to achieve local anti-histaminic action. *Levit* (1968) described a relatively inexpensive and easily constructed device for iontophoresis used in the treatment of palmar and plantar hyperhidrosis. *Gangorosa et al.* (1978) did conductivity studies to determine which could be the best candidate for iontophoretic delivery.

Investigations of iontophoresis as means for systemic delivery of drug has a relative recent origin.³

Mechanism of Iontophoresis

In the iontophoresis process, the current, beginning at the device, is transferred from the electrode through the ionized drug solution as ionic flow. The drug ions are moved to the skin where the repulsion continues moving the drug through the trans-appendageal structures and stratum corneum interstices via the aqueous pores. The larger the electrode surface, the greater the current the device must supply to provide a current density for moving the drug. Iontophoresis enhances transdermal drug delivery by three mechanisms:

- a) Ion-electric field interaction provides an additional force that drives ions through the skin, usually delivery of positively charged compounds is generally easier than negatively charged compounds as the skin itself possesses a net negative charge.
- b) The flow of electric current increases the permeability of the skin.
- c) Electro-osmosis produces bulk motion of solvent that carries ions or neutral species with the solvent stream.^{4,5}

Advantages

- 1) Avoid the risk and inconvenience of parenteral therapy.
- 2) Prevents variation in the absorption and metabolism of oral administrations.
- 3) Increases therapeutic efficacy by “bypassing” metabolism.
- 4) Reduces the chance of over or under dosing by continuous delivery of drug programmed at the required therapeutic rate.
- 5) Permits the use of a drug with a short biological half life.
- 6) Provides a simplified therapeutic regimen, leading to better patient compliance.
- 7) Permits a rapid termination of medication by simply stopping the drug input from the iontophoretic delivery system.³

Disadvantages

- 1) Drugs must be in aqueous solution and must be ionized form. Thus, many widely used drugs cannot be administered by this technique.
- 2) Additional ions act as a competitor for the ionic drug applied.
- 3) There is a limit to the quantity of medication that can be delivered, usually 5-10 mg/hr. To exceed this value, many medications would require a current sufficiently high to cause burns to the underlying skin.
- 4) The electrodes and its contact of drug applied to the skin act as a voltaic cell, resulting in the decreasing pH in the –ve electrode, limiting the duration of treatment. This situation robs the iontophoresis of its most valuable theoretical advantage: adjustable, long-term, non invasive delivery of medication.
- 5) The skin itself imposes a barrier to the delivery of some medications: introduction of ionized solutes with molecular weight greater than 8000 to 12000 results in a very uncertain rate of delivery.³

Factors affecting iontophoretic drug delivery system

Presence of extraneous ions: Other ions of the same charge can decrease the iontophoretic delivery of the drug ions because these ions compete with the drug for the iontophoretic flux.

Ionic strength: Higher ionic strength of the solution subjected to iontophoretic current resulted in decreased iontophoretic transport of the drug into the tissues as increase in ionic strength yields higher concentration of extraneous ions which compete for the electric current.

Ionised state of the drug: for eg. Lignocaine is not effective iontophoretically at a pH range of 3.4-5.2. With iontophoresis transdermal permeation is maximum at pH of 9.4 and above when it is mainly in the non-ionised state and at this pH, iontophoretic delivery is minimum.

Concentration: increased concentration of the charged molecule yields greater molecules in the tissues.

Current intensity: higher the intensity, greater then transport.

Polarisation: Direct current can cause polarisation whilst pulsed current can decrease tissue polarisation.

Shifts in pH in tissue and drug solutions: With metallic electrodes, shifts in pH are noted which can affect ionisation of the drug. pH changes in the tissue can cause injury due to migration of hydronium and hydroxyl ions produced by electrolysis. Separate buffered electrolyte solutions can be used which can prevent flow of ions into the tissue.⁶

Equipment and devices

The principle consideration for an iontophoretic device are: safety, convenience and reliability. The portability of device is also important. Many types of devices for the delivery of drugs, enzymes, dyes and other ions, have been employed.

Gibson and Cooke (1959) reported a device for iontophoresis of pilocarpine, device consist of DC-source, capable to delivering a current upto 15mA, and a voltage of 0-20 volts. Two modified electrodes were used.

Jenson (1964) reported iontophoretic toothbrush for delivering negatively charged drugs across the teeth.

Levit (1958) reported a device for the treatment of hyperhidrosis.

Hill (1976) reported device for treatment of hyperhidrosis with poldine methosulphate solution. Apparatus worked on 240 volts, 50 cycle AC.

Gangorosa and Park (1978) describe a dc source that was used to desensitize teeth. It could deliver currents between 0.4 and 1mA per minute.

Tapper (1981) disclosed a method and apparatus for applying iontophoretic treatment to a living body, which is provided by a unidirectional treatment current, periodically interrupted by a relatively short pulse of current in the opposite direction, to prevent the formation of bullae and vesicles in the skin being treated.

Ariuta et al. (1984) reported a device having a light weight and is capable of easy, direct application to the skin.

Groning (1987) reported an iontophoretic application system for transdermal or dermal administration of diphenhydramine HCl. It has pencil shaped carrier system, housing three 3-volts lithium batteries.^{3,7}

Biomedical applications

Iontophoresis has wide applications in Dermatology, Ophthalmology, ENT, Allergic conditions even in Cardiac and Neurological situations, but its greatest advantage is in the transport of protein or peptide drugs which are very difficult to transport transdermally due to their hydrophilicity and large molecular size.

Dermatology: In hyperhidrosis, especially palmar and plantar – probably by obstructing the sweat ducts. No side effects when compared to anti- cholinergics. Copper- iontophoresis for fungal infection and male contraception zinc for ulcers, iodine for reduction of scar tissues, iron/titanium oxide for tattoo removal. Histamine in allergy testing. In the diagnosis of cystic fibrosis to increase sweating by pilocarpine and confirm diagnosis by the concentration of sodium and chloride in the sweat. In scleroderma, for iontophoretic delivery of hyaluronidase.^{8,9}

Ophthalmology: Iontophoretic induction of various drugs like atropine, scopolamine, sulfadiazine, fluorescein, gentamycin etc.

ENT: For providing anaesthesia of the external ear canal and middle ear and in maxillo facial prosthetics surgeries.

Dentistry: To prevent dentin hypersensitivity and for providing local anaesthetic for multiple tooth extraction.

Neurophysiological and Neuropharmacological studies: As a research tool, micro-iontophoresis can be used to study neuro muscular junction, peripheral and central nervous system and smooth muscle preparations.

Delivery of drugs: Antihypertensives, anti-diabetics, anti-rheumatoids, hormones, vasodilators: Metaprolol, propranolol, insulin, methylcholine, bleomycin, steroids have all been introduced iontophoretically.

Musculo skeletal disorders: Magnesium sulphate for bursitis, Calcium for myopathy, Silver for c/c osteomyelitis, local anaesthetics and steroids into elbow, shoulder and knee joints.

Cardiology: Iontophoretic transmucosal drug delivery of anti-arrhythmic drugs which would avoid high systemic toxic levels is being done in animals.

For relief of pain: Iontophoretic histamine delivery as counter-irritant. In painless venipuncture. For post-operative pain relief. For iontophoretic delivery of local anaesthetics for referred pain .Anti-inflammatory drug delivery.

This is an area which has wide scope for expansion. We have seen the varied applications and the potential for improvement for this method of drug delivery. Further research is required to perfect this technique. There are several devices now available in all sizes and shapes to suit individual needs and ensure absolute safety. With even pencil shaped transdermal applicators now available for self administration, iontophoresis may prove to be an important alternative method of drug delivery in the near future.^{9,10}

Conclusion

Iontophoresis involves delivery of selected ions into tissues by passing a direct electrical current through a medicated solution and the patient. This method of drug administration have many advantages. Systemic side effects of drugs are significantly decreased because only minute amount of drugs are delivered, while a relatively high drug concentration is administered locally where it should achieve the maximum benefit. Patient acceptance is generally excellent, and fear of injection is eliminated.

Thus, iontophoretic transdermal delivery has the potential of improving the quality of drug therapy compared to conventional methods of oral drug administration or bolus intravenous injection because it can minimize dosage while maintaining a constant therapeutic level by continuous drug input.

Although there are a number of published accounts of the tissue levels achieved with specific drugs and treatment regimens, little efforts has been directed at relating these results to the transport properties of the membrane (skin) and the drug. Consequently, it is difficult to extrapolate these results beyond the specific systems tested.

Acknowledgement

I would like to thank Dr. D.K. Jain (Principal COP, IPS Academy, and Indore), Dr. Neelam Balekar (Vice Principal), Mr. Aakash Pawar and Mr. Pritesh Paliwal, who helped me a lot in writing this review. I would also like to acknowledge my father Dr. Shashikant Verma and mother Mrs. Manju Verma for providing me a great support during this whole work.

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