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IONTOPHORESIS – A NEW AGE TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Iontophoresis is the process of increasing the penetration of drugs into the skin by application of an electric current. . It is basically an injection without the needle. The drug is applied under an electrode of the same charge as the drug and another electrode placed at a neutral site on the body surface having a opposite charge to the drug particle. Electrical energy assists the movement of ions across the skin using the principle “like charges repel each other and opposite charges attract” This technique has three basic theories. Electrostatic Repulsion- Particles with similar charges repel each other. So anionic drugs are propelled out of the drug chamber and across the skin using a negatively charged electrode . Electric current enhances permeation- Skin is inhibited from performing protective barrier function.The current enhances water penetration into the stratum corneum (electro-osmosis) - Dissolved drugs are carried across the skin along with the penetrating water during iontophoresis. Iontophoresis is commonly used by physical therapists for the application of anti-inflammatory medications. Common diagnoses treated with iontophoresis include plantar fasciitis, bursitis and some types of hyperhydrosis. The most commonly-used form of testing for cystic fibrosis is the sweat test. Sweat-testing involves application of a medication (pilocarpine) that stimulates sweating to one electrode of an apparatus and running electric current to a separate electrode on the skin.

INTRODUCTION

The skin functions as a physical, chemical and microbial barrier to transport and is divided into the subcutaneous, dermis and epidermis. The outermost bilayer of the skin is stratum corneum, which is generally the primary barrier to transport across the skin. The skin permits passive absorption of lipophillic low molecular weight drugs in quantities that may be sufficient to cause local or systemic effects.[1, 2]

The drug must have some desirable physiochemical properties for penetration through stratum corneum. Drugs of shorter biological half-life and therapeutic value less than 10mg per day are suitable candidate for Transdermal drug delivery. Skin irritation or contact dermatitis due to the permeation enhancers is another limitation to the transdermal drug delivery. Also, the barrier function of the skin changes from person to person or from site to site in a same person only.

Transdermal 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.[3] 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.

Therefore, electrically assisted transdermal delivery can be used to enhance transport of active agents across the skin. Electrically enhanced delivery can be used for larger hydrophilic molecules, which is particularly advantageous for peptides and oligonucleotides drug administration.[4, 5]

HISTORY

The idea of applying electric current to increase the penetration of electrically charged drugs into surface tissues was probably organized by Veratti in 1947.[6] .Leduc did the first well- documented experiments at the beginning of the 20th century. [7]. Leduc demonstrated the introduction of strychnine and cyanide ions into the rabbits when the correct polarities were applied. Inchley also carried out similar experiments in 1921.[8] 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. The transdermal delivery of many ionized drugs at therapeutic levels is precluded by their slow rate of diffusion under a concentration gradient alone are now application with the help of iontophoretic technique and devices.

PRINCIPLES OF IONTOPHORETIC TREATMENT

Iontophoresis increases the penetration of electrically charged drugs into surface tissues by the application of an electric current.[9] Electrical energy assists the movement of ions across the stratum corneum according to the basic electrical principle of "like Charges repel each other and opposite charges attract". 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. The operator then selects a current below the level of the patient's pain threshold and allows it to flow for an appropriate length of time. The electrical current significantly increases the penetration of the drug into surface tissues by repulsion of like charges and attraction of opposite charges. The two classically considered prerequisites for iontophoretic treatment

Are that the drug must be charged (or modified to carry a charge) and that the disease process must be at or near a body surface.

TYPES OF IONTOPHORESIS TECHNIQUE

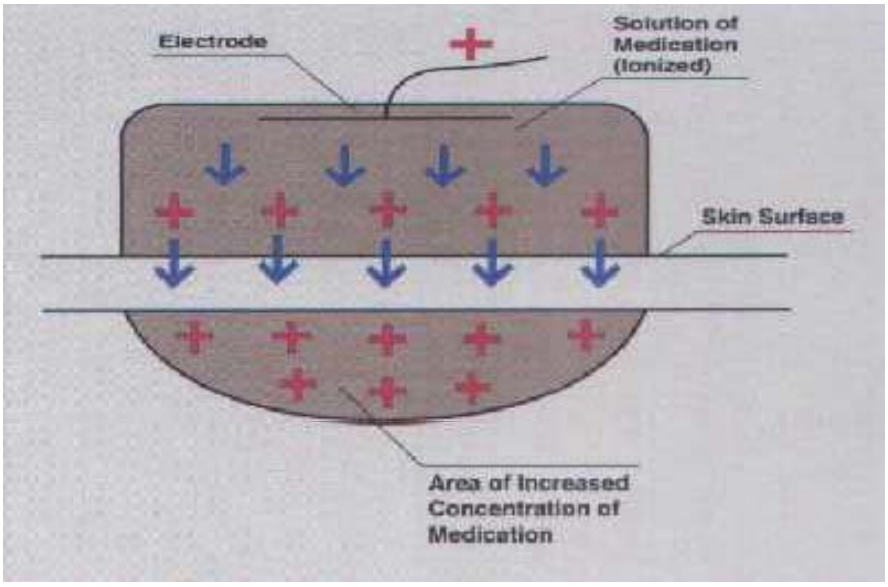
Voltage drop across a membrane driving force for the flux of ions through it opens up new type of approaches for transport of ionic drugs across skin. Iontophoresis is usually defined as either anodal (+) in which the positive anode is placed in the solution applied to the epidermis and negative cathode is placed in the solution applied to the epidermis and negative cathode is placed in the dermal receptor solution, or cathodal (-), in which the electrode location are reserved. Anodal (+) iontophoresis is facilitated by the movement of a caution from the donor to the receptor, whereas cathodal iontophoresis implies the movement of an anion from the donor to receptor[10].

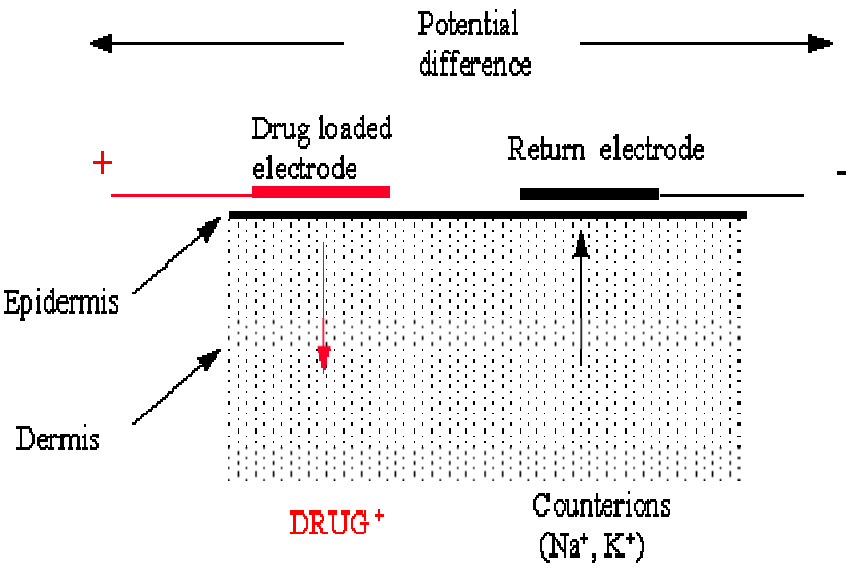
Anode = positively charged electrode

- Lower concentration of electrons
- Repels positively charged ions
- Attracts negatively charged ions
- Accumulation of positively charged ions in a small area creates an alkaline reaction

Cathode = negatively charged electrode

- Highest concentration of electrons
- Repels negatively charged ions
- Attracts positively charged ions
- Accumulation of negatively charged ions in a small area creates an *acidic* reaction





Iontophoretic delivery of a positively charged drug through the skin

MECHANISM OF IONTOPHORESIS

A typical iontophoresis device consists of DC voltage delivery system and electrodes. Wires are then connected between the unit and the active and passive electrodes, and the unit set for current and time. In the beginning of iontophoresis process, the current 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 [11]. 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, (b) The flow of electric current increases the permeability of the skin, and (c) electro-osmosis produces bulk motion of solvent that carries ions or neutral species with the solvent stream.

Electro osmotic flow occurs in a variety of membranes and is in the same direction as the flow of counter-ions. It may assist or hinder drug transport. Since human skin is negatively charged above pH 4, counter ions are positive ions and electro-osmotic flow occurs from anode to cathode. Thus, anodic delivery is assisted by electro-osmosis but cathodic delivery is retarded because of the electro-osmotic flow, transdermal delivery of a large anion (negatively charged protein) from the anode compartment is more effective than that from the cathode compartment [12].

ADVANTAGES OF IONTOPHORETIC DRUG DELIVERY SYSTEM

1. It is a non-invasive technique thus reduces the risk of infection.
2. Reduces chances of overdosing or under dosing by providing continuous delivery of drug programmed at the required therapeutic rate.
3. Provide predictable and extended duration of action.
4. Reduces frequency of dosage.
5. Self-administration is possible.
6. Iontophoretic delivery prevents contamination of drugs reservoir for extended period of time.
7. Provides a pain free treatment for those who are unable to receive injections.
8. Increases therapeutic efficacy by passing hepatic first pass metabolism.
9. Permits the use of drug with a short biological half-life and prevents variation in absorption and metabolism reactions as seen with oral administration.

10. Permits a rapid termination of medication, by simply stopping the drug input from the iontophoretic delivery system.

DISADVANTAGES OF IONTOPHORETIC DRUG DELIVERY SYSTEM

1. Drugs must be in aqueous solution and ionized. Therefore, many widely used drugs cannot be administered by this technique.
2. Skin itself imposes a barrier to delivery of some medications.
3. Limit to the quantity of medication that can be delivered, usually 5 to 10mg/hr.
4. An excessive current density usually results in pain
5. Electric shocks may cause by high current density at the skin surface
6. Possibility of cardiac arrest due to excessive current passing through heart.
7. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.
8. High molecular weight 8000-12000 results in a very uncertain rate of delivery.
9. The high current density and time of application would generate extreme pH, resulting in a chemical burn[1]
10. Ions present in parent rally administered drugs such as sodium chloride and sodium citrate are act as a charged carriers or active competitors for the drug applied.

FACTOR INFLUENCING IONTOPHORETIC DRUG DELIVERY

1. PHYSICOCHEMICAL VARIABLES

These include the charge, size, structure and lipophilicity of the drug. The drug should be water soluble, low-dose and ionizable with a high charge density. Smaller molecules are more mobile but large molecules are also iontophoresable.

2. FORMULATION FACTORS

These include the drug concentration, pH, ionic Strength and viscosity.

1. Drug concentration: Increasing drug concentrations results in greater drug delivery to a certain degree.

2. Ionic strength: If buffer ions are included, they compete with the drug for the delivery, decreasing the quantity of drug delivered,

especially since buffer ions are generally smaller and more mobile than the larger active drug.

3. PH: The pH of the solution can be adjusted and maintained by larger molecules, such as ethanolamine: ethanolamine hydrochloride rather than the smaller hydrochloric acid and sodium hydroxide. An increase in ionic strength of the system will also increase the competition for the available current, especially since the active drugs are generally potent and present in a smaller concentration than these extraneous ions.

4. Viscosity: The migration of the drug is inversely related to the viscosity.

3. BIOLOGICAL FACTORS

These factors involve the skin to which the electrodes are applied; its thickness, permeability, presence of pores, etc. Sweat glands are the most significant path

for the conduction of charges into the skin. This was demonstrated by Papa and Kligman, when methylene blue introduced into the skin via iontophoresis entered sweat glands in a punctuate pattern and outlined the sweat pores.[14]

4. ELECTRONIC FACTORS

1. CURRENT

The current can be direct, alternate or pulsed, and can have various waveforms, including square, sinusoidal, triangular and trapezoidal. The more complex forms may not be of much advantage as direct current is most commonly used. In a recent study, alternating current (AC) iontophoresis showed better results than conventional constant current DC iontophoresis. Constant conductance AC iontophoresis showed reduced flux drift and less skin to skin variability compared to conventional constant current DC iontophoresis.[13]

2. ELECTRODES

The electrode materials used for iontophoretic delivery are to be harmless to the body and sufficiently flexible to apply closely to the body surface. The most common electrodes are aluminum foil, platinum and silver/silver chloride electrodes used for iontophoretic drug delivery. A better choice of electrode is silver/silver chloride because it minimizes electrolysis of water during drug delivery.

The positioning of electrodes in reservoir depends on the charge of the active drug. The distribution of drug within the skin depends on the size and position of electrodes. They are usually selected according to individuals needs. Larger electrode areas introduce the greater amounts of drug but lesser current density is tolerated to the skin in a non-linear

manner. Metal electrodes touching to the skin produce burns with much lower current in composition to padded electrodes. A loose contact between the padded electrode and skin also produce burn due to uneven distribution of current. The safe current density varies with the size of electrodes.[15, 16]

APPLICATION OF IONTOPHORETIC TECHNIQUE

1. It can be used for treatment of hyperhydrosis (increased perspiration), dental caries, & muscular disorders.
2. It can also be used for fungal infections such as tineapedia.
3. Insulin and vasopressin drugs have been successfully delivered through the intact skin by applying a noninvasive iontophoretic delivery technique.[17 , 18]
4. Peptide drug like various amino acid derivative, tripe tides, THRH, calcitonins can also be administered.[19]
5. Iontophoresis has become an important, new, safe and effective technique for enhancing drug delivery in diverse application such as local neuralgia, anesthesia, antiviral, anticancer, and anti-inflammatory therapies.
6. Iontophoresis is one of the methods, which can be used for facilitated delivery of chemicals, e.g. Metallic and nonmetallic ions, vasodilators and local anesthetics.[20,21]
7. Iontophoresis patch technology can be used to deliver drug solution for dermatology.
8. Used for broad range of skin disease e.g. Psoriasis, acne, skin cancer, ageing, wounds, ulcers and burns.
9. Iontophoresis may also be important for intra- ocular delivery of high concentration of medications .Application of low current to the eye through iontophoresis replaces the intolerable hourly application of the antibiotics needed to achieve reasonable concentration of the drug in the corneal tissue in the case of microbial/fungal keratitis. Anti-inflammatory and anti-glaucoma drugs can also be administered in similar manner.[22,23]
10. The application for propranolol, oxytoxin, verapamil, azidothymidine, butophanol tartrate and metoprolol tartrate has considerably enhanced bioavailability as compared to passive diffusion. [24,25]

CONCLUSION

Iontophoresis is a non-invasive drug delivery system and offers many

advantages. Systemic side effects of drugs are significantly decreased, patient acceptance is excellent and fear of injection is eliminated thus, iontophoresis transdermal delivery has the potential of improving the quality of drug therapy compared to conventional methods of oral dosage administration or bolus intravenous injection because it can minimizes dosage while maintaining a constant therapeutic level by continuous drug input.

Iontophoresis have been widely used in dentistry, ophthalmology and diagnostic applications. Iontophoresis is a promising drug delivery technique that, at present, requires a greater focus on research directed towards the study of macroscopically, electrical, and molecular mechanism involved in this process.

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