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REVIEW ARTICLE

An Injection without the Needle: Iontophoresis

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ABSTRACT

Penetration of healthy skin by drugs in solution is normally very limited due to the excellent barrier function of the stratum corneum (the most superficial layer of the skin). This barrier can be overcome using iontophoresis: by applying an electrical potential (voltage) across the skin, drug ions become the charge carriers that convey the electrical current through the skin. Iontophoresis is a technique which uses an electric current to deliver a medicine or other chemical through the skin. In popular (lay) terms it is sometimes called "an injection without the needle". Iontophoresis can be defined as a non-invasive method of propelling high concentrations of a charged substance, (normally a medication or bioactive agent), transdermally by repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged active agent and its vehicle. 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.

KEY-WORDS: Iontophoresis, Current, Ions, Transdermal

INTRODUCTION:

The skin is the largest organ in the body and, with its large surface area, represents an attractive route for drug administration. Several transdermal systems have been developed and marketed for the relief of pain, contraception, hormone replacement, motion sickness, hypertension and angina. Transdermal drug delivery systems provide distinct benefits due to elimination of hepatic first-pass effects, reduction in systemic side effects by decrease in initial dose size and increased patient compliance. However, development of formulations and systems for transdermal delivery has been hindered by poor tissue permeability – predominantly in the outermost layer of the skin – known as the stratum corneum (1).

Iontophoresis is the introduction of various ions into the skin by means of e1ectricity. This definition, however, should be expanded because many nonionic materials such as polypeptides can be delivered into the body by iontophoresis. The term iontophoresis is simply defined as ion transfer (ionto = ion; phoresis = transfer). Physical therapists use iontophoresis with the objective of delivering a locally higher, therapeutic concentration of an ion or other medication, while minimizing the systemic concentration caused by circulatory removal of the material from the area. The use of iontophoresis has fluctuated over the years, partly due to concerns about chemical burns of the skin that can accompany iontophoresis treatment and the lack of research demonstrating the efficacy of the technique. Recently, there has been resurgence in the use of iontophoresis, particularly for the delivery of anti-inflammatory medications. Interest has also grown in the use of iontophoresis for the percutaneous delivery into the body of systemically active drugs and maintenance of therapeutic levels. This approach has been termed "controlled release (2, 3)."

BASIC PRINCIPLES (4, 5):

In order to 'drive' the ions into the tissues, a direct (Galvanic) current needs to be employed. Some authorities suggest that the current needs to be continuous, though others have argued that so long as the current is monophasic in nature, a pulsed application can be used. Continuous (classic) DC is most commonly used in practice. Essentially, the substance to be driven into the tissues needs to be ionic in nature, and must be placed under the electrode with the same charge (i.e. positively charged ions placed under the positive electrode (Anode) and the reverse for a negatively charged ion). The positively charged chamber, called the anode, will repel a positively charged chemical into the skin. The negatively charged chamber, called the cathode, will repel a negatively charged chemical into the skin.

Conventionally, the electrode under which the ionic solution is placed is called the active electrode (other terms include treatment electrode or delivery electrode). The other electrode, which is used to complete the circuit, is most commonly called the dispersive, indifferent,

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inactive or return electrode. For consistency in this document the terms active and indifferent electrodes will be used. Ions with a polarity which is the same as that of the stimulating electrode are repelled into the skin.

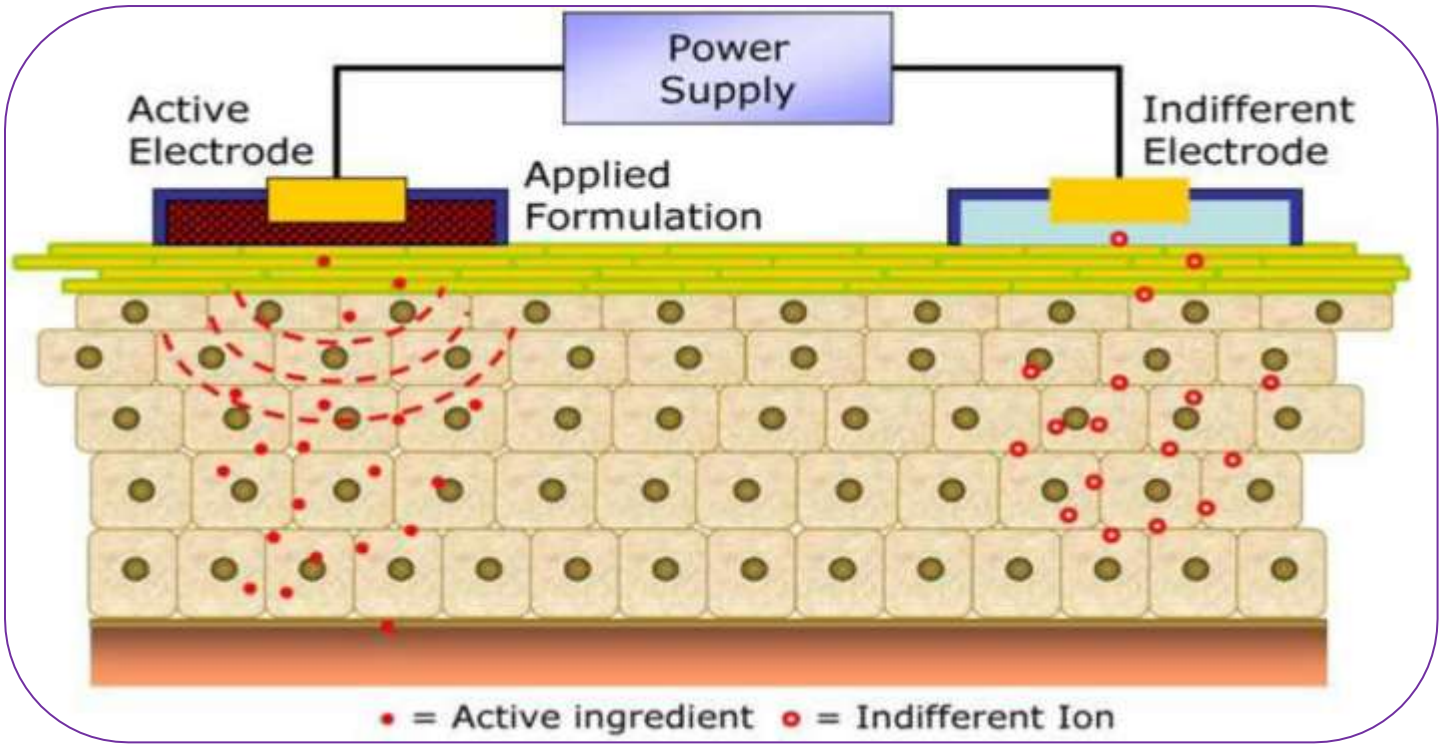

Figure 1: Basic Principles of Iontophoresis (4)

It is assumed that the effects of the treatment are attributed to the delivered ions and not the direct current - though interestingly, this basic premise has not actually been fully established. Given the wealth of evidence in favour of various DC applications, including a recent resurgence of High Voltage Pulsed Current (HVPC) and the developing use of microcurrent based therapies; it would be surprising if the DC current had no effect in its own right.

The ions are driven into the skin via the pores - hair follicles, sweat gland ducts - rather than through the stratum corneum per se (the stratum has a high resistance, thus limited current passes through it - the ducts are lower resistance, will allow greater passage of current, thus the route of preference). The ions (ionic solution) used will depend on the therapeutic effects which are intended. The table in this document identifies some of the more commonly employed solutions, their use and the electrode under which they need to be placed in order for the iontophoretic effect to be achieved. These substances range from tap water through to steroid based medicines and the regulations concerning their use will vary from country to country depending on prescription and therapist autonomy.

ADVANTAGES (2, 6):

1. Increases therapeutic efficacy by bypassing hepatic "first-pass" elimination-the reduction in the amount of the drug entering the systemic circulation, due to metabolism by the liver as the drug passes through the hepatic circulation after absorption from the gastrointestinal tract.

2. Avoids the risks and inconveniences of parenteral (injection/intravenous) therapy.

3. Reduces the chance of overdosing or under dosing by providing continuous delivery of the drug, programmed at the required therapeutic rate.

4. Prevents the variation in the absorption and metabolism seen with oral administration.

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

6. Permits the use of a drug with a short biological half-life because (1) the drug is delivered directly to the target organ without the need to circulate and recalculates in the blood or (2) the drug is delivered directly into the bloodstream without delays due to absorption through the gastrointestinal tract.

7. Permits a rapid termination of administration of the medication, if needed, by simply turning off the iontophoretic delivery system.

8. Provides a simplified therapeutic regimen, leading to better patient compliance.
9. Iontophoresis turned over control of local anesthesia delivery in reducing the pain of needle insertion for local anesthesia.
10. Self-administration is possible.
11. Reduce frequency of dosage.
12. Provide predictable and extended duration of action.

DISADVANTAGES (6, 7, 8):

1. An excessive current density usually results in pain.
2. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.
3. The safe current density varies with the size of electrodes.
4. Burns are caused by electrolyte changes within the tissues.
5. This change in pH may cause the sweat duct plugging perhaps precipitate protein in the ducts, themselves or cosmetically hyperhydrate the tissue surrounding the ducts.
6. The high current density and time of application would generate extreme pH, resulting in a chemical burn.
7. Electric shocks may cause by high current density at the skin surface.
8. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.
9. High molecular weight 8000-12000 results in a very uncertain rate of delivery.
10. Possibility of cardiac arrest due to excessive current passing through heart.

FACTORS AFFECTING THE IONTOPHORESIS PROCESS (9-11):

Factors affecting the IP process include: the drug concentration, drug salt form, pH of the drug micro environment, the current intensity and duration, competing ions in the electrode solution/matrix, stability of the drug during the IP process, the type of matrix containing the drug and current density. Additionally, patient anatomical factors and the presence and extent of inflammation can influence the depth of drug penetration.

1. Drug Concentration: Increased uptake by the skin during and after IP with an increase in drug concentration has been reported. This is generally true until a plateau level is reached at which no further increase in flux is observed.

2. 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 suitability of a drug for IP. The salt form of drugs must be considered along with the pH of the solution for determining the amount of drug in the ionized state.

3. pH of the Drug Micro environment: Laboratory findings vary on the effect of pH and drug behavior. According to the Henderson-Hasselbalch equation, pH is the determining factor governing the amount of drug present in the ionized state. For optimum IP, it is desired to have a relatively large proportion of the drug in the ionized state. However, this must be counterbalanced with delivery of a drug at a pH that is tolerable and safe for the patient.

4. Current Intensity and Duration: From Faraday's Law we know that in an electrolytic solution the transported quantity of electricity depends on the strength of the current and the duration of its passage. Thus, this law would suggest that the same number of ions should be transported at different strengths of current if the time for current flow is inversely related to their strengths. However, generally speaking, we also know that in some cases, higher current may deliver more drug than lower current, possibly due to induced changes in skin permeability by the higher current, resulting in a greater flow of drugs. The rate at which the ions are introduced into the body with various current strengths can play an important role. When the current is stronger, more ions penetrate at one time. The strength of the current used also depends on the sensitivity and tolerance of patient.

5. Competing Ions in the Electrodes: Electrical current is carried by positive and negative ions in solution. There is no major distinction between ions of the same charge even though they are composed of different chemical elements. Therefore, solutions for IP should be as pure as practical and generally contain as few extraneous substances as possible. Drug solutions should be prepared with purified water (deionized, distilled, reverse osmosis). It is has been shown that the presence of excipients in dosage forms, i.e. preservatives in injections as well as compounds used as external buffers, will alter the amount of drug delivered. In vitro, the total current will be carried by drug ions along with the same charges as drug ions in the donor cell plus the counter ions present in the receptor cell. Therefore, the competing ions in the donor cell and the counter ions in the receptor cell will be affecting the actual current carried by the drug moiety. During IP, there is a shift in pH due to hydrolysis of water which may result in a loss of efficiency of drug transfer due to presumably

competing ions. Buffers may be built into the electrode to minimize this effect, but the buffer materials should be bound, or immobile, and not released for IP transport, as they would then compete with the active drug.

6. **Stability of the Drug during the IP Process**: The drug undergoing IP must be stable in the solution environment up to the time of IP and also during the iontophoretic process. Oxidation or reduction of a drug not only decreases the total drug available but the degradation compounds, if they possess the same charge as the drug ion, will compete with the drug ion and reduce the overall transmembrane rate of the drug.

7. **Type of Matrix Containing the Drug, Gel Vs. Solution**: The migration of the drug under the influence of the electrical current, will be different as the matrices are different. This can be related to differences in viscosities, material electrical charge and porosities.

8. **Current density**: Current density is the quantity of current delivered per unit surface area. The following criteria should be considered in selecting proper current densities for IP: (1) the current should be sufficiently high to provide a desired drug delivery rate; (2) it should not produce harmful effects to the skin; (3) there should be a quantitative relationship between the flux and the applied current; and (4) there should be electrochemical stability of the drug.

9. **Patient Anatomical Factors**: Patient anatomical factors that influence the depth of penetration that are variable from patient to patient include skin thickness at the site of the application, presence of subcutaneous adipose tissue and the size of other structures, including skeletal muscle. Additionally, the presence and severity of inflammation can influence drug penetration due to the increased temperature (which may increase penetration rate) and the elevated level of blood and fluids present that may serve to transport the drug throughout the body.

APPLICATION DEVICES:

There are many specific (dedicated) machines sold which are solely designed to deliver this type of treatment. Several are for patient home use (especially for the treatment of hyperhydrosis). Most modern multifunction devices will include iontophoresis type currents in their menu options. Additionally, the so called 'wireless' application devices are gaining popularity, eespecially for home use. The delivery system is 'self contained' in that the electrodes (self adhesive) and stimulator are in a single housing which the patient applied to the affected area. The electrode patch is preconfigured and delivers a smaller current than is normally employed in the department or clinic (typically 0.1mA). The patch is applied for 12 - 24 hours (depending on the intended dose) after which time, it is removed and disgarded (they cannot be reused) (4).

Figure 2: Examples of dedicated iontophoresis devices (4)

Figure 3: Examples of multimodal devices which include iontophoresis facilities (4)

Figure 4: Recently developed iontophoresis device (12)

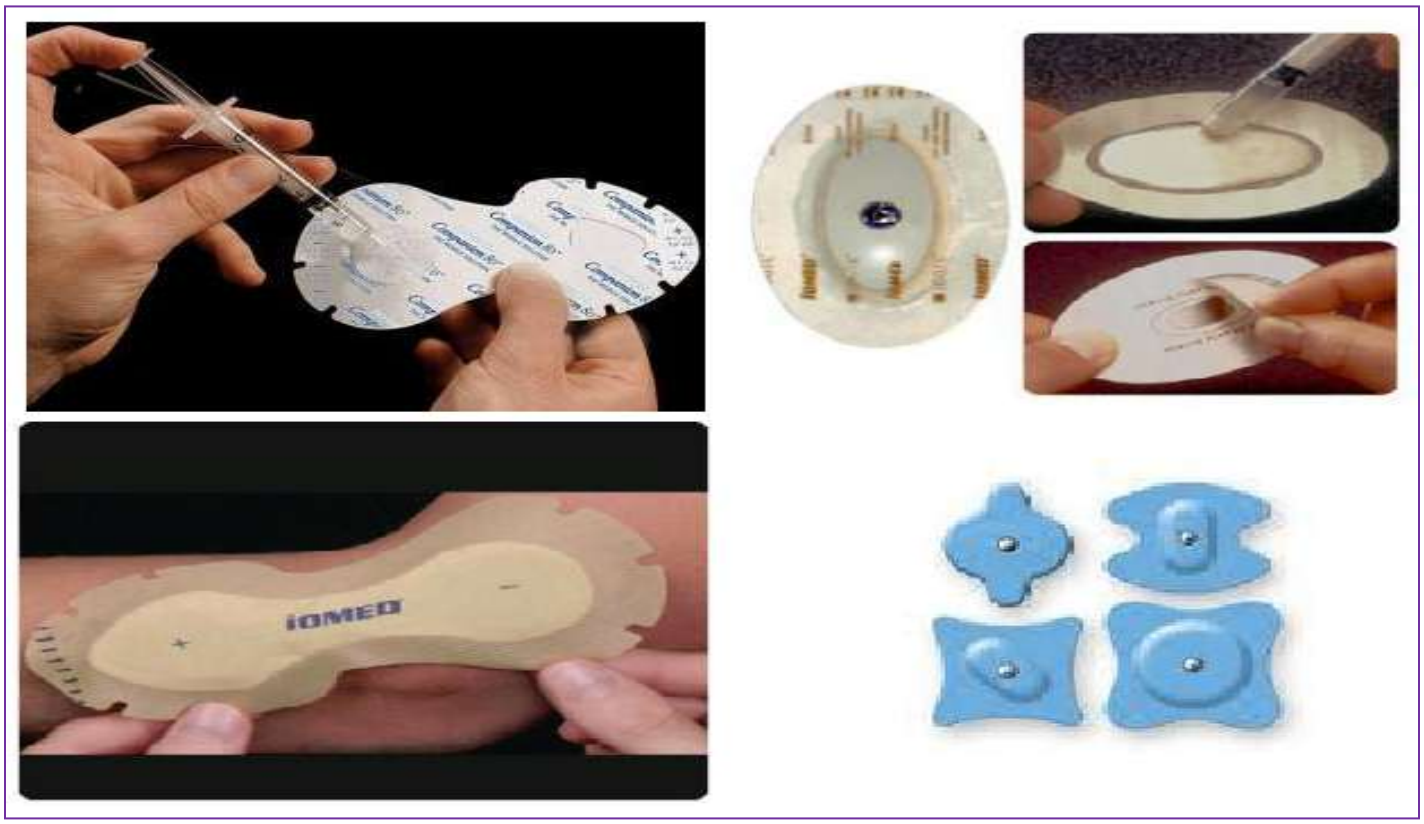

Figure 5: Examples of commercially available iontophoresis electrode systems (4)

APPLICATION OF IONTOPHORESIS (6, 13, 14):

1. Topical delivery:

The ability to control the delivery rates of drugs by changes in current makes iontophoresis an attractive technique to use. Yamashita et al. studied the efficacy of iontophoretic delivery of calcium for treating hydrofluoric acid-induced burns.

2. 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.

3. 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.

4. Treatment of hyperhidrosis:

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 that is 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 of 15–20 mA to each palm or sole for 30 min per session for 10 consecutive days, followed by one or two maintenance sessions per week.

5. 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.

6. Dentistry:

Dentistry, probably to an even greater extent than physical therapy, has used iontophoresis. Beginning in the late 19th century, dentists applied local anesthetics to their patients prior to oral surgical 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 charged fluoride ions; (2) treatment of oral ulcers ("canker sores") and herpes orolabialis 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.

7. Peptide delivery:

This is the most promising applications of iontophoretic transdermal delivery. Transdermal delivery itself offers the advantages of bypassing first pass metabolism and gastrointestinal degradation as well as patient compliance over the existing oral and parenteral routes of administration for peptide delivery. An additional advantage that it offers specifically for proteins and peptides is the avoidance of strong proteolytic conditions as found in the gastrointestinal tract.

8. Non-invasive monitoring of glucose:

Electro osmotic flow generated by application of low level current has been used for extraction of glucose through the skin. As the direction of glucose flow is in the opposite direction (in outward direction in skin) to conventional iontophoresis, it is called reverse iontophoresis. This property in combination with in situ glucose sensors has been used in Gluco Watchw Biographer. This device allows noninvasive extraction glucose across the skin, allowing a diabetic's glycemia to be evaluated every 10 min over several hours.

CONCLUSION:

Iontophoresis dramatically enhances both the rate of release and the extent of penetration of the salt form of the drugs. Without iontophoresis, such charged species are largely incapable of transdermal penetration due to the skin's lipophilic nature. Iontophoresis is gaining wide popularity as it provides a non invasive and convenient means of systemic administration of drugs with poor bioavailability profile, short half life and with multiple dosing schedules. Iontophoresis, in comparison to oral route, definitely provides benefits of improved efficacy and/or reduction in adverse effects. The major advantages of iontophoretic delivery system which makes its future use hopeful on large scale are the accurate control over drug input kinetics and optimization of drug input rates. In the future, this system might be used to deliver therapeutic proteins or vaccines transdermally. Using iontophoresis, transdermal delivery of insulin, thyrotropin-releasing hormone, leuprolide, gonadotropin- releasing hormone, arginine-vasopressin and some tripeptides has been demonstrated.

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