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Iontophoresis: Anemergingapproachtotransdermal drug delivery

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Abstract:*Iontophoresis is a non-invasive method used to boost high concentration of a charged substance, generally medication or bioactive agents, transdermally by repulsive electromotive force using a small electrical current applied to an iontophoretic chamber containing a similarly charged active agent and its vehicle. For effective delivery via iontophoresis, the positively charged chamber, termed anode, will repel a positively charged chemical, while the negatively charged cathode, will repel a negatively charged chemical into the skin. In the presence of an electric field, electro-migration and electroosmosis are the dominant forces in mass transport. Two principal mechanisms by which iontophoresis enhances drug delivery across the skin are: electrorepulsion and electroosmosis. Electrorepulsion is the direct effect of the applied electric field on a charged permeant. The second mechanism, electroosmosis, results from the fact that the skin supports a net negative charge at physiological pH. Iontophoresis have been applied both clinically in treatment and diagnoses of various diseases and in some other non-clinical cases.During iontophoresis, a medical device delivers mild electrical currents while the affected body part is submerged in water. The currents are often delivered to the hands, feet, or armpits to block sweat glands temporarily. Some people feel a slight tingling sensation during the procedure, but the electrical current isn't strong enough to bring about shock. Iontophoresis is most commonly used to treat hyperhidrosis disorder, a condition that results in persistent and excessive sweating. This sweating may occur in certain situations, such as during warm weather or physical activity, or without any trigger at all. It can also be caused by other medical conditions, such as hyperthyroidism or menopause. Aside from treating hyperhidrosis, iontophoresis may also be used to treat sports injuries by delivering anti-inflammatory medications directly into the skin.*

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I. Introduction

Discovering new medicines coupled with redesigning the modules and means to transport these medicines into the body are more lucrative and time consuming tasks [Schuetz *et al*., 2005]. However, 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 site becomes complicated if each medication were not to be delivered in an optimal and preferred manner to the individual patient [Chien, 1990]. Oral ingestion has long been the much convenient and commonly employed route of drug delivery. This is also because there is more flexibility in dosage form design for the oral route than there is for parenteral route. In contrast, continuous intravenous infusion is recognized as a superior mode of drug administration not only to bypass hepatic "first-pass" metabolism, but also to maintain a constant and prolonged drug level in the body [Burnette and Ongpipattanakul, 1987]. This mode of administration is advantageous to both direct entry of drug into the systemic circulation and control of circulating drug levels. However, such mode of drug administration entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of administration.

The novel drug delivery systems (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 or to improve therapeutic index. Research soon followed on ways the drug levels could be modulated and extended to derive more benefits and lower the toxicological risks from the dosage of drug [Harris, 1995; Riviere and Heit, 1997]. Novel delivery systems for non-traditional routes of administration were subsequently conceived, constructed and put to test [Arunachalam and Gunasekaran, 2002]. In the last three decades a number of modern technologies including targeting concepts have emerged for successful delivery of bio-actives. The limitations have been overwhelmed by these modern technologies, which are providing effective local as well as systemic drug levels at desired sites with improved safety profiles. The increased attention on patient 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 [Riviere and Heit,

1997]. Patients often forget to take their medicine, and even the most faithfully compliant get tired of swallowing pills, especially as part of daily dosage. 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.

Transdermal drug delivery is an interesting approach to treat skin diseases and to avoid pain and increase patient compliance in cases where a systemic delivery is required. However, the stratum corneum, which is the outermost skin layer and the main barrier for permeation of drug strongly, protects the body from the entrance of substances, especially those hydrophilic (Lee *et al*., 2018). The possibility of delivering bioactive molecules through the skin represents an interesting alternative to oral or parenteral injection. This so-called transdermal drug delivery bypasses the gastrointestinal tract and thus prevents the first-pass effect, is painless and allows self-administration (Münch et al., 2016). Besides transdermal delivery, the skin is the main route of choice for the treatment of dermatological disorders and for local anesthesia (Goyal *et al,* 2016). Topical drug delivery can potentially eliminate the need of systemic administration of drugs, reduce the total drug dose required and thus reduce adverse off-target effects (Goyal *et al.,* 2016). Therefore, topical delivery is useful in the treatment of skin inflammations, photoaging, microbial and fungal infections and also skin cancer (Prow *et al.*, 2016). Topical or transdermal delivery requires that the drug overcomes the stratum corneum (SC), which is the main skin barrier, to reach the viable epidermis, where most of the cutaneous disorders are found, or the systemic circulation. For topical delivery, the main challenge is the balance between the penetration of the drug through the SC and its buildup in the skin to ensure suitable therapeutic concentration. Generally, small molecules can penetrate the SC easily or transpose the epidermis by the appendices. However, for high molecular weight molecules, such as peptides, siRNA and DNA, penetration into or through the skin remains a challenge (Goyal *et al.,* 2016). This can be explained by the "500 Dalton Rule", which describes that a drug can penetrate the SC and be delivered through the skin if its molecular weight is less than 500 Daltons and if it is hydrophobic (Bos and Meinardi, 2000).There are different methods of transdermal drug delivery namely:

Chemical methods involve the use of chemical enhancers to disturb skin-structure (Williams and Barry, 2004; Lane, 2013) and facilitate drug delivery into the skin.

Biological methods involve the use of skin metabolism inhibitors through the synthesis of bio-convertible pro-drug.

Physical method involves the use of an external force applied to a formulation, or to a drug delivery system, placed over the skin. This external force can disrupt the skin barrier or simply facilitate the delivery of the drug from the formulation with consequent increase in permeation of the drug. Among the various approaches available, some of them can be highlighted such as iontophoresis, which consists on the application of low intensity electric current (Gratieri *et al*., 2008), sonophoresis, with application of low-frequency ultrasound (Polat et al., 2010) and microneedles, which are minimal invasive needle-like microprojections (Moffatt *et al*., 2017). Although these strategies have been extensively studied to facilitate transdermal drug delivery (Moffatt, 2017; Münch et al., 2017; Lee et al., 2018), in the last decade there is an increasing interest in their use for some dermatological treatments, such as skin cancer. Herein, we aim to discuss the concepts involved in the cutaneous application of iontophoresis (physical) method of transdermal drug delivery and its influence on topical skin treatments.

Iontophoresis is an effective technique for physically facilitating transport of solutes (ionic therapeutic agents) across skin by the application of a low-level electric current for both local and systemic effects. Iontophoresis technique helps to circumvent or transpose the SC and achieve percutaneous absorption (penetration of substance into various layers of skin and permeation across the skin into systemic circulation) (Robert, 2004) following penetration and permeation of drug molecules into the skin. Thus, full knowledge of the skin structure is crucial to the understanding of the mechanism that governs the iontophoresis process.

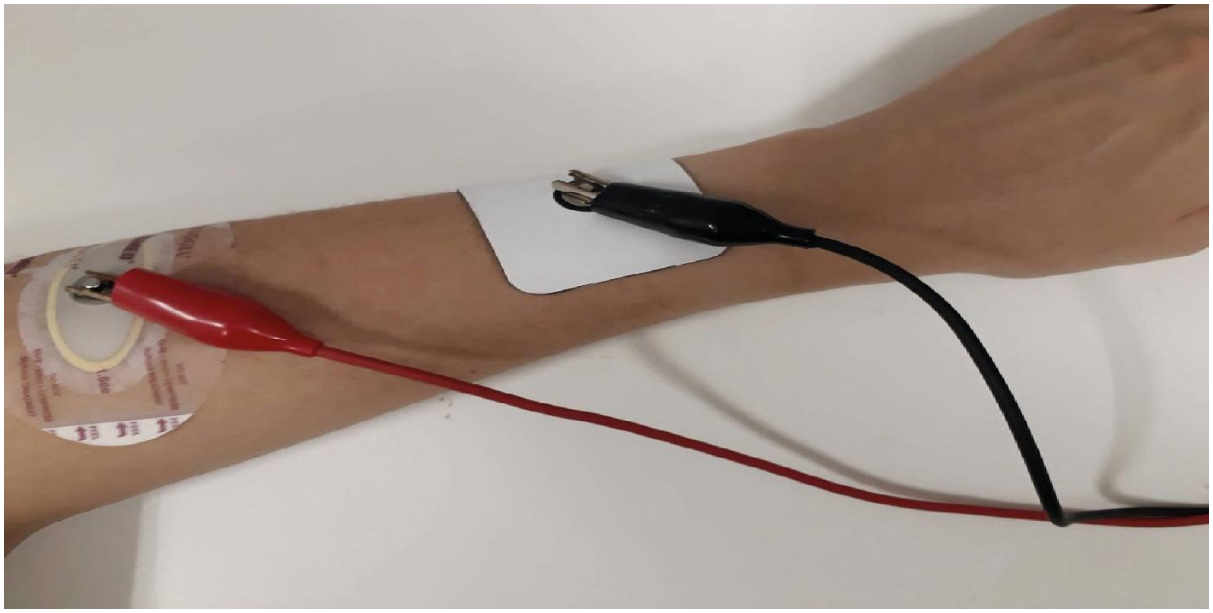

Figure 1: Experimental setup for *in vivo* iontophoresis using Iogel®

SKIN STRUCTURE

The skin covers and protects the body, separating the internal environment of the outer environment. It is the largest organ of the human body, representing around 16% of body weight (Santana, 2003). The human integumentary tissue is divided into: [1] epidermis, [2] dermis and [3] hypodermis. The surface of the epidermis is called the stratum corneum (Costa, 2009). The stratum corneum (Figure 1) is an important component of the skin layers, responsible for preventing loss of body fluids, and for blocking the entry of exogenous substances (Cestari, 2005). The physicochemical properties of the skin enable percutaneous absorption of topically applied medications; however, most of the medications used need to overcome the barrier imposed by the stratum corneum (Oliveira, et al., 2004) in order to guarantee their pharmacological effects (Martins et al., 2007). The three pathways that a medication uses to overcome the stratum corneum are:

1. Intracellular, where medications diffuse around corneocytes,
2. Transcellular, where medications diffuse directly through the corneocytes, and
3. via appendices, an alternative route for medications that diffuse through the hair follicles, sebaceous and sweat glands (Gratieri, 2008).

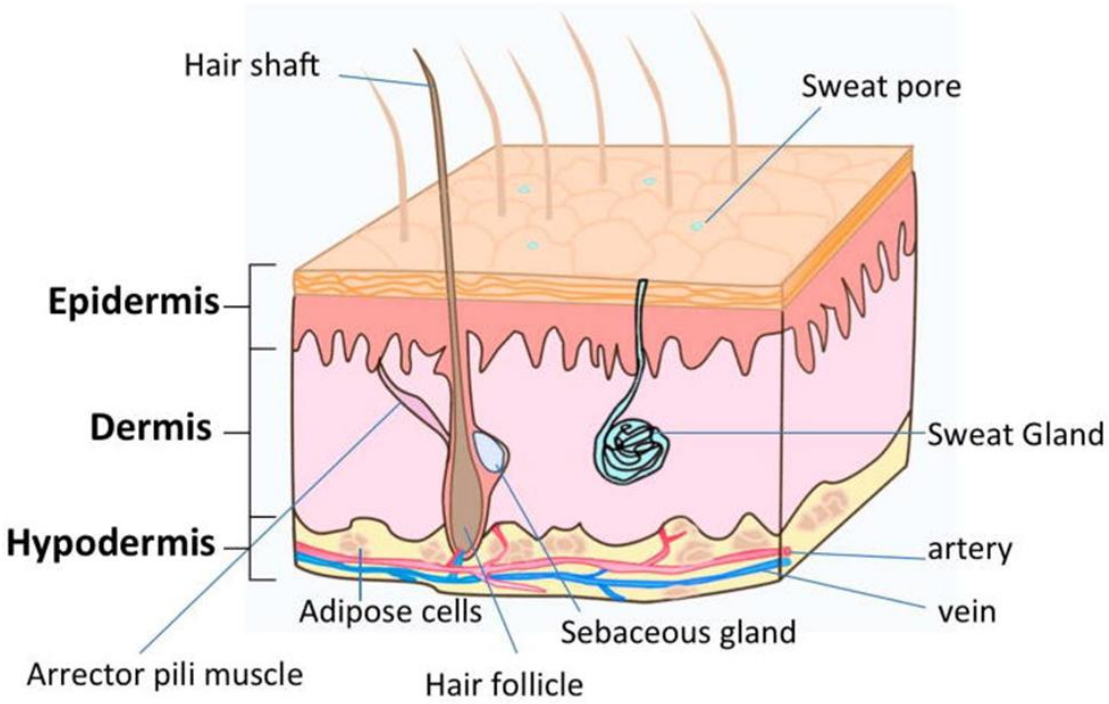

Figure 2: Skin Anatomical Structure (Costa, 2009)

Historical background of iontophoretic process

Iontophoresis, derived from the Greek "ionto" meaning 'ion' and "phoresis" meaning 'to bear,' is a process that allows increased penetration of ionized molecules across or into the tissue by application of low electric current. 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.

The idea of applying electric current to increase the permeation of electrically charged drugs into surface tissues was probably originated by Pivati in 1747. In the eighteenth century Galvani and Volta combined the knowledge that electricity can move different metal ions and the movement of the ions produced electricity. In the beginning of the twentieth century Leduc introduced the term ionotherapy and formulated laws regarding this process.

The first reported study on transdermal iontophoretic delivery of insulin for systemic effect was attempted to deliver regular soluble insulin to human volunteers. Iontophoresis of commercially available insulin was done on eight volunteers, but negative results were obtained even after repeating the study on three occasions. However, the investigators were able to deliver a highly ionized monomeric form of insulin to one pig and observed a decline in blood glucose levels and an increase in serum insulin levels [Stephen et al., 1984]. Okabe et al., [1986] applied a new technique for the transdermal delivery of beta-blockers and carried out transdermal permeation of metoprolol in human volunteers. No detectable skin damage was observed in the study.

Glass et al., [1979] conducted the most widely quoted research on iontophoresis; applied it to multiple joints on a Rhesus monkey then excised the underlying tissue to determine depth of penetration. And found that therapeutic concentrations of the drug at depths of up to 1.7 cm. The vascular network is located just below the layer of skin; therefore the drugs can be effectively delivered by this route. Many other researchers have contributed to the field of iontophoresis with great success.

MECHANISMS OF IONTOPHORESIS

The major iontophoretic mechanisms of enhancing drug flux through skin are:

- Iontophoresis (electrorepulsion, electromigration or Nernst plank effect)
- Electroosmotic flow
- Damage effect (current induced increase in skin permeation)

Two principal mechanisms by which iontophoresis enhances drug delivery across the skin are: electrorepulsion and electroosmosis. Electrorepulsion is the direct effect of the applied electric field on a charged permeant. The second mechanism, electroosmosis, results from the fact that the skin supports a net negative charge at physiological pH (Masada, 1989; Charro and Guy, 1998).

Iontophoresis is a non-invasive method used to boost high concentration of a charged substance, generally medication or bioactive agents, transdermally by repulsive electromotive force using a small electrical current applied to an iontophoretic chamber containing a similarly charged active agent and its vehicle. For effective delivery via iontophoresis, the positively charged chamber, termed anode, will repel a positively charged chemical, while the negatively charged cathode, will repel a negatively charged chemical into the skin. In the presence of an electric field, electro-migration and electroosmosis are the dominant forces in mass transport (Cullander, 1992).

These movements are measured in units of chemical flux, commonly $\mu mol/cm^2$ h. This technique is based on the general principle that like charges repel each other. Thus, during iontophoresis, if delivery of a positively charged drug (D^+) is desired, the charged drug is dissolved in the electrolyte surrounding the electrode of similar polarity, i.e. the anode in this example (Singh and Bahtia, 1996). On application of an electromotive force the drug gets repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body. Communication between the electrodes along the surface of the skin has been shown to be negligible, i.e. movement of the drug ions between the electrodes occurs through the skin and not on the surface. When the cathode is placed in the donor compartment of a Franz diffusion cell to enhance the flux of an anion, it is termed cathodal iontophoresis, and for anodal iontophoresis the situation would be reversed. Iontophoresis uses a low current, and patients' have little or no sensation during the procedure (Siddiqui et al., 1985)

The basic mechanisms of ionic/molecular transport across the skin by iontophoresis is illustrated in figure 2. Like charges repel each other, hence the charged ion is repelled by a similarly charged electrode and absorbed through the skin. The skin being negatively charged at physiological pH acts as a cation selective membrane and favours movement of cations through anodal iontophoresis. Anodal iontophoresis also causes convective motion of the solvent occurring in response to movement of counter ions. This process of electroosmosis is involved in the motion of neutral compounds as well as positively charged ions. Because of

the complex nature of iontophoretic delivery, a number of attempts have been made to define the rate of iontophoretic delivery.

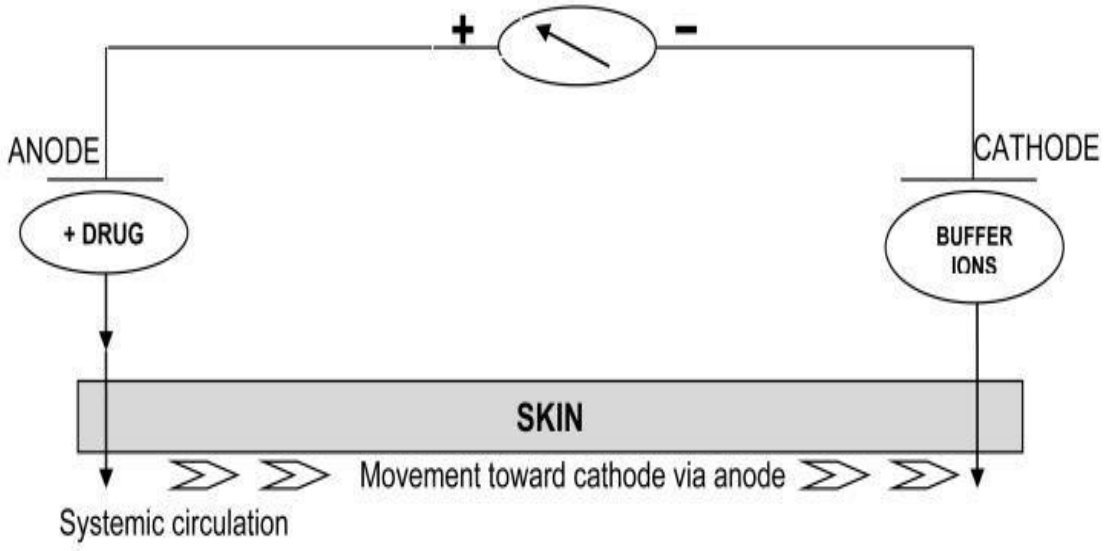

Fig Figure3: Mechanism of iontophoresis.

Merits

1. It is non-invasive technique could serves as substitute for chemical enhancers (Srinivasan and Higuchi, 1990)
2. Eliminate problems like toxicity, adverse reaction and formulation related problems.
3. Prevent variation in the absorption of TDDS (Bodde et al., 1989)
4. Eliminate chance of over and under dosing by continuous delivery of drug programmed at the required therapeutic rate.
5. Provide predictable and extended duration of action.
6. Reduce frequency of drug.
7. Self-administration is possible (Yogeshvar, 2004)
8. Provide simplified therapeutic regimen, leading to better compliances.
9. Permit rapid termination of the modification.
10. It may permit lower quantities of drug compared to use in TDDS.
11. TDDS of many ionized drug at therapeutic levels was
12. Precluded by their slow rate of diffusion under a
13. Concentration graduation, but iontophoresis enhanced flux of ionic drugs across skin under electrical potential gradient
14. It is important in systemic delivery of peptide/protein-based pharmaceuticals, which are very potent, extremely short acting and often require delivery in a circadian pattern to simulate physiological rhythm, e.g. Thyrotropin releasing hormone, somatotropine, tissue plasminogen activators, interferons, enkephalin, etc. (Phipps et al., 1989)
15. Provide predictable and extended duration of action.
16. A constant current iontophoretic system automatically adjusts the magnitude of the electric potential across skin, which is directly proportional to rate of drug delivery.
17. An iontophoretic system also consists of an electronic control module which would allow for time varying of free-back controlled drug delivery Iontophoresis turned over control of local anesthesia delivery in reducing the pain of needle insertion for local anesthesia (Bellantone, 1986).
18. By minimizing the side effects, lowering the complexity of treatment and removing the need for a care to action, iontophoretic delivery improve adherence to therapy for the control of hypertension
19. Iontophoretic delivery prevents contamination of drug reservoirs for an extended period of time.

Demerits

1. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate (Sanderson, 1989)
2. An excessive current density usually results in pain burns are caused by electrolyte changes within the tissue (Moliton and Fernandez, 1989)
3. The safe current density varies with the size of electrodes (Miller, 1987)

4. The high current density and time of application would generate extreme pH, resulting in a chemical burn. This change in pH may cause the sweat duct plugging and perhaps precipitate.
5. Protein in the ducts or hyperhydrate the tissue surrounding the ducts (Miller, 1987)
6. Electric shocks may be caused by high current density at the skin surface.
7. Possibility of cardiac arrest due to excessive current passing through heart. 8. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.
9. High molecular weight compounds result in a very uncertain rate of delivery.

FACTORS AFFECTING IONTOPHORESIS PROCESS

The factors influencing iontophoretic delivery of a drug can be broadly classified into operational and biological factors [Turner and Guy, 1997; Banga et al., 1999). These factors are;

Operational factors;

I. Composition of formulation:

- Concentration of drugs
- pH of the donor solution
- Ionic strength
- Presence of co-ions

II. Physicochemical properties of the permeant:

- Molecular size
- Charge
- Polarity
- Molar weight

III. Experimental conditions:

- Current density
- Current profile
- Duration of treatment
- Electrode material
- Polarity of electrode

Biological factors

I. Intra ant inter subject variability
II. Regional blood flow
III. Skin pH
IV. Conditions of skin

A. Operational Factors

I. Composition of Formulation:

Concentration: Concentration of drugs is one of the most important factors affecting iontophoretic processes. The effect of the concentration has been studied on a number of drugs. An increase in concentration was shown to increase the apparent steady state flux of a number of drugs e.g., AVP (Lelawongs et al., 1989), butyrate (Delterzo et al., 1989), diclofenac sodium (Koizumi et al., 1990), metoprolol (Thysman et al., 1992), atenolol HCl [Jacobsen, 2001], ketorolac [Tiwari and Udupa, 2003], rotigotine [Nugroho et al., 2004] and dopamine agonist 5-OH DPAT [Nugroho et al., 2005]. All these drugs showed a proportional increase in flux with an increase in concentration. With drugs like benzoate [Bellantone et al., 1986] and LHRH [Miller et al., 1990], a modest increase was observed. But this is not the general observation since, an increase in concentration increases flux upto a point, after which the flux becomes independent of the donor concentration. This is probably due to the charge saturation of the aqueous conducting pathways of skin also called boundary layer saturation [Sanderson et al., 1989]. Methylphenidate showed a little change in flux when concentration was increased beyond 0.1M [Singh et al., 1997].

pH: Since iontophoresis is widely used for peptide delivery, pH plays a vital role and it determines the ionization of peptides, which depends upon isoelectric point and respective pKa of charged amino acid. Moreover, skin permeability is also dependent upon pH e.g., AVP (pI- 10.8) showed maximum flux when donor having a wide range of pH (4-8) were used [Iwakura and Morimoto, 1991; Morimoto et al., 1992] but calcitonin (pI-6.5) showed optimum flux at pH 4.0 and not at higher pH [Morimoto et al., 1992]. 5-OH DPAT showed enhanced flux when pH was increased from 3 to 5 but not at higher pH [Nugroho et al., 2005]. In case of leuprolide (LHRH agonist) a two fold increase in flux at pH 7.2 was observed than at pH 4.5 (Kochhar and Imanidis, 2004). Since pH influences the charge on protein, polarity of electrodes is an important factor to be taken into consideration during drug delivery e.g. anodal delivery of insulin is preferred [Pillai et al., 2000] but

below its isoelectric point [Siddiqui et al., 1987] whereas in case of pilocarpine a moderate pH of 5.98 is required to achieve maximum permeation [Huang et al., 1995]. Thus, the optimum pH for iontophoretic delivery of a compound is one where it exists predominantly in an ionized form. The effect of pH of aqueous vehicle on rate and extent of iontophoretic delivery of lidocaine was investigated. The rate was found to be maximum when the drug was in an ionized form [Siddiqui et al., 1985]. Thus, pH is an important factor governing the iontophoretic delivery of drugs. Moreover, it also influences the chemical stability of the drug involved.

Ionic strength & presence of other ions: In iontophoresis the main aim is that the drug ion should carry maximum charge across the membrane. It follows that an increase in ionic strength will decrease drug delivery, as extraneous ions compete with the drug ions. The buffering agents used to maintain pH of the donor medium is a source of co-ions. These co-ions are generally more mobile and smaller in size than the drug ions itself and can dominate the penetration into the skin thereby causing a decrease in transdermal flux of the drug. Many peptides widely studied for ionic strength showed a higher flux occurring at low electrolyte concentration [Fu et al., 1993; Craane-Van et al., 1994]. Similarly, drugs like ketorolac showed increased flux with decrease in ionic strength [Tiwari and Udupa, 2003]. A 50% reduction in benzoate flux occurred when an approximately equimolar amount of NaCl was added to the donor compartment [Miller et al., 1990]. Salicylic acid flux was found to decrease with the increase in concentration of HEPES buffer [51] and 5-OH DPAT flux decreased with addition of NaCl [Nugroho et al., 2005]. But occasionally an increase in ionic strength leads to an increased flux e.g., iontophoresis facilitated an increased skin permeation of AVP as the ionic strength of donor solution increased [Nair et al., 2000].

II. Physicochemical Properties

Molecular size and molecular weight: The molecular size of the solute is a major factor governing its feasibility for iontophoretic delivery and hence the amount transported. When the iontophoretic delivery of carboxylate ions was studied, flux for acetate was found to be more than that of hexanoate and dodecanoate. This suggests that smaller and more hydrophilic ions are transported at a faster rate than larger ions [Miller et al., 1987; Miller and Smith, 1989]. Many studies correlating flux as a function of molecular weight have been conducted and it was concluded that for electro repulsive iontophoresis, when all other conditions were kept constant, transport of compounds decreased with increase in molecular weight (chlo-ride>amino acid>nucleotide>tripeptide>insulin) (Burnett and Ongpipattanakul, 1987; Green et al., 1991; Green et al., 1992; Langkjaer et al., 1994; Vander-Geest et al., 1996). But due to the use of advanced techniques like iontophoresis, electroporation and phonophoresis, delivery of even large molecule like peptides is possible now.

Charge: Charge on a molecule is an important physicochemical property governing iontophoretic transport, since the sign of the charge determines the mechanism by which iontophoresis will proceed e.g., electrorepulsion or electron repulsion and electroosmosis. Although the transport of cations has been shown to be better than anions for amino acids and peptides, this however is not so simple because an increase in charge will require pH to be decreased, which inturn shall directly decrease the electroosmosis and electrotransport process. An increased positive charge on peptide, causes it to bind tightly to the membrane creating a reservoir which in turn can decrease the rate at which the steady state flux will be achieved [Berner and Dinh, 1998].

Polarity: Generally, the compounds which are hydrophilic are considered ideal candidates for optimum flux e.g., nalbuphine and its ester showed an increased flux as the lipophilicity of the compound decreased [Sung et al., 2000].

III. Experimental Conditions

Current strength: Since current can easily be controlled by the use of electronics, it is a convenient means to control delivery of drugs to the body. However, a large increase beyond the permissible limits causes irritation and can damage the skin. A linear relationship has been observed between the apparent flux of a number of compounds and the applied current. Methylphenidate showed a linear relationship between the applied current and its iontophoretic flux [Singh et al., 1997]. A linear increase in the flux with current has also been found for TRH [Burnette and Marrero, 1987], verapamil [Wearley et al., 1989], GRH [Miller et al., 1990], ketorolac (Singh et al., 1997) and diclofenac [Hui et al., 2001]. In general, 0.5 mA/cm2is often stated to be the maximum iontophoretic current which should be used on human beings [. Miller et al., 1987].

Current profile: Mostly, in the studies conducted on animals in vitro, current is kept constant and very low voltage of about 10V should be applied.

Duration of treatment;

The transport of drug delivery depends on the duration of current applied in iontophoretic drug delivery (Abramowitsch et al.,1946).The iontophoretic penetration of drug linearly increased with increasing application time.The skin permeation of arginine vasopressin achieves higher plateau rate and in case of insulin delivery, 2-3 fold reduced the blood glucose levels with increase in duration of iontophoretic application (Chien et al., 1989).

Pulsed current:

The persistent use of direct current (DC), proportional to time, can reduce the iontophoretic flux because of its polarization effect on the skin (Lawler et al., 1960). This can be overcome by the use of pulsed DC which is a direct current delivered in a periodic manner [Banga, and Chien, 1988]. During "off stage" the skin gets depolarized and returns to the initial polarized state. However, Bagniefski and Burnett showed that enhanced skin depolarization can decrease the efficiency of drug transport, if the frequency of pulsed current is very high [Bagniefski and Burnett, 1990]. A two fold increase in the transdermal flux of vasopressin was observed when pulsed current was used in vivo in rabbits [Singh et al., 1998]. Enhanced transport of proteins and peptides has been reported using pulsed DC e.g., insulin [Chien et al., 1990]. But in many cases like sufentanil [Préat and Thysman, 1993], fentanyl [Thysman et al., 1994] and ketorolac [Tiwari and Udupa, 2003] a decreased flux was observed when pulsed current was used as compared to constant direct current.

Electrode material: Iontophoretic studies have been conducted using both platinum wire and Ag/AgCl wires. However, platinum electrodes or other inert electrodes like nickel or stainless steel have been found to cause pH drift and gas bubbling due to decomposition of water and thus causing production of H+ and OH-ions [Lelawongs et al., 1989] in the following manner:

Anode: H_2O $2H+ + 1/2\ O_2 + 2e-$

Cathode: $H_2O + e-$ $OH- + 1/2\ H_2$

Thus, Ag/AgCl electrodes with redox potential lower than that of water which help to maintain electroneutrality at both anode and cathode have been used for this purpose. Phipps et al. [Phipps et al., 1989] studied the electrode material selection in optimizing the delivery of lithium across polyvinyl alcohol (PVA) hydrogel membrane. They showed use of platinum anode in donor caused a pH decrease due to production of hydronium ion as shown above, which are more mobile and no efficient delivery of lithium was observed while the use of Ag/AgCl electrodes in place caused no pH drift and a significant increase in lithium flux almost double of the above case was observed.

B. Biological factors

I. Intra and inter subject variability;

Iontophoresis reduces intra and inter-subject variability in the delivery rate. This is an inherent disadvantage with the passive absorption technique. Experiments in vivo iontophoretic give support for clinical findings that there are small differences in the flux rate following transdermal iontophoresis between males and females, as well as between hairy and hairless skin (Gangarosa et al., 1978).

II. **Regional blood flow:** During iontophoresis, the dermal blood supply determines the systemic and underlying tissue solute absorption. Blood supply however, does not appear to affect the drug penetration fluxes through the epidermis during iontophoretic delivery. Cross and Roberts [Cross and Roberts, 1995] showed that solute in the upper layer of the skin following iontophoresis was comparable in anaesthetized rats and sacrificed rats. It can thus be presumed that the blood did not affect the penetration through the epidermis since the latter has no blood supply.

III. **Condition of skin:** In iontophoresis, skin condition also affects the penetrating properties of permeant. Roberts et al., studied the in vivo passive diffusion of methyl salicylate using skin from different areas of the human body and observed the following rank order: abdomen> forearm> instep> heel> planter, for all subjects [Roberts et al., 1982]. Feldman et al., showed that the passive diffusion of hydrocortisone occurred maximally from the area with numerous hair follicles while lesser in area with thickest stratum corneum [Feldman and Maibach, 1967].

TYPES OF IONTOPHORETIC SYSTEM

The system of drug delivery via iontophoresis can be classified in accordance to the modification and improvement done in this system, which allows the uniform and predictive drug release in an effective manner¨

- Reverse iontophoresis
- Pulsative/switching Iontophoresis
- Iontophoresis and electoporation combination

Reverse iontophoresis

Reverse iontophoresis, a technique in which low electric current is applied to draw intestinal fluid through the skin, is widely applied these days in devices meant for diagnostic application. This provides a convenient and non-invasive method for sampling of body fluids so as to permit simultaneous measurement of the desired substance in the body fluid and thus to monitor them efficiently. The reverse iontophoretic process applies to continuously monitor the glucose level in the blood for e.g. Glucowatch®, which is a system that provides a needleless means of monitoring blood glucose levels in diabetic patients and uses an electrical signal

which is proportional to the amount of glucose in the extracellular fluid. This provides a feasible method for rapid, linear extraction of phenylalanine and for easy detection (by instruments like biosensors) of monitoring diseases like phenylketonuria (Merino et al., 1999). This technique not only provides non-invasive sampling but also provides filtered samples free from large molecules with ease of operation. However, this technique is useful for less tedious sampling. For it to be successful, it needs a very sensitive analytical method since the amount extracted is very low. For e.g. Caffeine, theophyline; lithium; phenytoin are successfully tried using this approach.

Pulsatile/switching iontophoresis

Many studies have been conducted where instead of using constant DC iontophoresis, DC in the form of short pulses have been used (Tierney et al., 2002).

Iontophoresis and electroporation combination

Iontophoresis can also be combined with other skin penetration enhancing techniques like electroporation, which involves the application of high voltage (> 100 V) pulses for short duration (μs-ms) to increase the permeability through the skin. Electroporation is applied before iontophoresis, which causes the creation of permeablized skin because of exposure to high pulses voltage (Huang et al., 2005). Thus, when applied after electoporation, iontophoresis helps in extending the permeabilized state of the skin, resulting in the rapid onset (which is a drawback of iontophoresis alone) and sometimes increased flux (Prausnitz et al., 1993). The increased transport by electroporation caused by creation of electro pores as well as local field induced electrophoretic drift. Fang et al., studied the effect of electroporation on the delivery of buprenorphine and showed that on application of 300 V or 500 V pulses increased the buprenorphine flux by several folds over passive transport of it; e.g. drugs like Salmon calcitonin (SCT) and PTH combination; Tacrine hydrochloride have been successfully tried using this approach (Banga et al., 1999)

Other synergistic approaches with Iontophoresis

Iontophoresis in conjunction with chemical enhancers: Although, the use of iontophoresis results in much higher drug delivery if compared with conventional passive transdermal delivery, it still has limitations as a technique. Chemical enhancers can be used in combination with iontophoresis to achieve even higher drug penetration. In addition to increasing transdermal transport, 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 combined effects of enhancers and electrically assisted delivery depend on the physico-chemical properties of the penetrant, enhancer and their behavior under the influence of an electric field. Occasionally, the use of chemical enhancers was reported to result in reduced flux compared with using iontophoresis alone (Choi et al., 1999 and Chesnoy et al., 1999). However, more often synergistic effects have been reported such as those with fatty acids, and terpenes and others.

Iontophoresis conjunction with sonophoresis; Synergy between low-frequency ultrasound and iontophoresis would be expected since the techniques both enhance transdermal transport although through different mechanisms (Mitragotri et al., 2004). As a matter of fact, the disruption of SC lipid bilayer by the application of ultrasound can be utilized by further use of iontophoresis to increase transdermal drug transport to a greater degree. This combination has been found to enhance transdermal transport better than any of the single treatments alone. Iontophoresis combined with low frequency ultrasound was used in the transdermal delivery of sodium nonivamide acetate (SNA) (Fang et al., 2002). Pretreatment of the skin with low frequency ultrasound (0.2 W/cm2, 2 h) alone did not increase the skin permeation of SNA. The combination of iontophoresis (0.5 mA/cm2) and sonophoresis increased transdermal SNA transport more than iontophoresis alone.

Iontophoresis in conjunction with microneedles: Few studies have reported the combination of iontophoresis with microneedle technologies. This combination may provide the possibility of macromolecule transdermal delivery with precise electronic control. Lin et al. designed a Macrofluxw®and iontophoresis combined transdermal ISIS 2302 (Lin et al., 2001). The Macrofluxw®array, 2 cm2, had a microprojection density of 240/cm2 and a needle length of 430μm. Macrofluxw® and iontophoresis combined system was made by assembling the Macrofluxw® array, a drug reservoir, a membrane, a conductive gel and the iontophoretic electrode.

Iontophoresis in conjunction with ion-exchange materials: For this combined technique, experimentally the ion exchange materials were initially immersed into drug solution for 3h to overnight. Afterward, such a drug-loaded device (e.g. disc, a bundle of ion exchange fibers or hydrogel filled with ion exchange resins) was transferred to the donor part of a diffusion cell for in vitro or in vivo tests (Jaskari et al., 2000, Kankkunenet al., 2002 and Kankkunen et al., 2002). The successful in vivo delivery of therapeutic dosage of tacrine, an anti-Alzheimer's disease agent, (Kankkunen et al., 2002).

SELECTION CRITERIA FOR DRUG CANDIDATE

Transdermal route of drug administration has certain inherent difficulties that make it unsuitable for a large number of drugs. The selection of suitable candidates is an important step for success of transdermal research (Brain et al., 2002).

Ideal characteristic drug should possess for the successful delivery through this approach:

- A transdermal drug delivery system (TDDS) should not cover an area more than 50 cm^2 and the daily dose is of order of a few mg.
- The effective concentration of the drug should be low, presumably in the ng/ml.
- The half-life ($t_{1/2}$) of the drug should be short.
- The active ingredients should not cause any skin toxicity or irritation.
- As the diffusion of drug through polymer as well as skin is dependent on molecular size, the drug of low molecular size is preferred.
- 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, are suitable candidates for transdermal delivery.
- Tolerance to the drug must not develop under the near zero-order release profile of transdermal delivery.
- The candidate drug should have adequate hydrophilic and lipophilic balance to negotiate the lipid barrier of stratum corneum before being partitioned into the aqueous viable tissue.

Table 1: List of drugs investigated recently for iontophoretic delivery

DRUGS	INDICATION	REFERENCES
Thiocolchicoside	Enhanced flux of the drug over passive control.	(Yamashita et al.,2001)
Rotigotine	Flux increased with drug concentration. With co –Ions viz.TEA, flux of rotigotine increased while TBA Showed no effect on flux.	(Nugroho et al., 2004)
Leuprolide(LHRH agonist)	Iontophoretic permeation was found to be double at pH 7.2 than at pH 4.5 (increased transference number was observed).	(Kochhar et al., 2004)
5-Amino Levulinic acid (Ala) &its methyl ester (m-Ala).	Ala- steady state -10-12 h. Flux-65 nmole/cm2 .m -Ala -steady state -2.5-4.0 h flux-145 nmole/cm2	(Merclin et al.,2004)
Gentamycin	Concentration achieved in cornea and aqueous humour was 12-15 times higher than the topical eye drop.	(Esther et al., 2004)
Salbutamol	Enhanced flux from the vehicle	(Nolan et al., 2003)
Dextran sulphate	Cumulative amount fluxed from cathode was approximately 300 times moreover passive and from anode it was 15 times more	(Badkar et al., 2002)
Diclofenac	Full plasma concentration achieved in 1 h. Drug deliverywas proportional to current (371± 141 µgm /lt at 0.5 mA/cm2 and 132 ± 62 µ gm/ lt at 0.2 mA/ cm2)	(Hui, et al., 2001)
Atenolol hydrochloride	Delivery of atenolol hydrochloride increased with increase in donor concentration	(Jacobsen, 2001)
Buprenorphine	8 fold increase in delivery by anode than cathode	(Bose et al., 2001)
Piroxicam	10 fold increased permeation.	(Curdy et al., 2001)
Timolol maleate (TM))	Iontophoretic transport highest in human skin and lowest in rabbits	(Kanikannan et al., 2001)

APPLICATION OF IONTOPHORESIS

Iontophoresis have been applied both clinically in treatment and diagnoses of various diseases and in some other non-clinical cases in the following ways;

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 (Yamashita et al., 2001).

Treatment of hyperhydrosis: 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) (Hill et al., 1981). Other proposed mechanisms include impairment of the electrochemical gradient of sweat secretion and a biofeedback mechanism (Karakoc et al., 2002). 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 (Hill et al., 1981).

Ophthalmology: Because it is a non-invasive system for transport of molecules and because it has no restrictions regarding the number of applications, iontophoresis has been used for ocular treatment to deliver antibiotics into the eye by Behar-Cohen et al. (1997). Using its electromotive action, iontophoresis-based treatment has the ability to carry various types of medications to different eye tissues, without any risk to the integrity of the patient's eye (Behar-Cohen et al., 1997). In an experimental study (Frucht-Pery et al., 2004), the use of gentamicin sulphate with iontophoresis was tested on rabbit cornea. In this study after application of gentamicin sulfate associated with iontophoresis, the rate of gentamicin penetration was influenced by the intensity of the current and/or the length of iontophoresis application. The major dis-advantages presented in this type of treatment (eye) are possible burns resulting from repetitive electrical contact of electrodes near the eye (Fialho and Cunha Júnior, 2007). Behar-Cohen et al. (1997) evaluated the application of iontophoresis with ocular application of dexamethasone in rats with parenteral administration of the same drug. The results revealed that treatment with iontophoresis produced the same treatment efficacy as parenteral application, but without presenting systemic adverse effects, because it was a topical application.

Treatment of hemophilia: Iontophoresis is used with the drug histamine bicloridate in palliative treatment for hemophilia patients in order to promote absorption of bruises and analgesia. It should be noted that in some cases, histamine is irritating to the patient's skin. In this case, the simple application of galvanizing properties provided by iontophoresis appeared amenable to treatment (Say et al., 2008).

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 (Karakoc et al., 2002).

Dentistry: Gangarosa described the use of iontophoresis for three basic applications in dentistry: (1) treatment of hypersensitive dentin (e.g., 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. (3) the application of local anesthetics to produce profound topical anesthesia, as is done in some physical therapy applications (Potts et al., 2002).

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 GlucoWatchw Biographer (Cygnus Inc., Redwood City, CA, USA) (Potts et al., 2002). This device allows noninvasive extraction of glucose across the skin, allowing a diabetic's glycemia to be evaluated every 10 min over several hours.

Peptide delivery: This is the most promising application 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 (Pannatier et al.,1978). The delivery of oligopeptide, vasopressin, with transdermal periodic iontotherapeutic system (TPIS) (Chien.,1991).

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 (Mattar, 2010).

Treatment of leprosy: The technique involves the use of ionization with potassium iodide followed by 2% sodium salicylate ionization. Sixteen applications in patients with leprosy were performed three times a week, over a period of twenty to fifty sessions. Eight patients had reversal of paralysis and normalization of gait. In these cases, the duration of paralysis varied from one month to a maximum of two years (Belda and Reginato, 1967).

Treatment of Geloidfibroedema: Geloidfibroedema, popularly and mistakenly called "cellulite" is a frequent and aesthetically relevant dysfunction, especially for the female population (Milani et al., 2006). It is described (Da Cunha et al., 2007) that treatment using iontophoresis and galvanization (use of electric current without pharmaceuticals) shows remarkable results in the treatment of cellulite reduction.

To reduce the level of LDL and sub-cutaneous adipose tissue; research conducted by applicationof abdominal electrolipophoresis, together with iontophoresis associated with a pharmaceutical consisting of turmeric gel aimed to evaluate the lipid profile and levels of fat in the abdomen, before and after applications. The study was conducted in eighteen women aged 21 to 51 years old, who were sedentary and without dietary restriction. The data collected showed satisfactory results regarding the use of electrolipophoresis along with turmeric in decreasing the levels of the lipid profile (LDL), as well as the effective decrease of subcutaneous adipose tissue (Zanin et al., 2008).

Anaesthesia: Local anesthesia is often required in conditions like superficial wound excisions, local skin biopsies, eyelid surgery, abscess incision, or in patients who are averse to the use of hypodermic needles. The disadvantages of injecting a local anesthetic include pain, distortion of tissue, potential systemic absorption. The usefulness of iontophoresis to achieve local anesthesia has been well documented. The advantages of iontophoresis induced anesthesia include no tissue distortion, adequate local and little systemic concentrations of the drug and the procedure is painless. Based on a controlled study employing lidocaine, Gangarosa reported that skin anesthesia was best obtained with solutions containing 1% and 4% lidocaine with addition of epinephrine prolonged the duration of anesthesia (Gangarosa, 1981).

Facilitation of underlying deep tissue penetration of compounds: The use of iontophoresis to facilitate underlying deep tissue penetration of drugs after topical application will be most beneficial in the treatment of osteoarthritis, soft-tissue rheumatism, tendonitis and other deep rooted local inflammatory conditions associated with sports injuries or other minor accidental injuries. This has been demonstrated by the penetration of dexamethasone in tissues below the applied site in monkeys [Glass et al., 1980].The drug was observed at sufficient tissue depths including tendinous structures and cartilaginous tissue. Iontophoresis of water soluble glucocorticoids dexamethasone, hydrocortisone and prednisolone up to a depth of 1.25 cm below the applied was also demonstrated by some researchers (Murray et al., 1963).

Treatment of edema: Hyaluronic acid, a gelatinous substance that exists in many body tissues, is a major constituent of the "ground substance" of connective tissue. It restricts diffusion of certain substances through the tissues. Hyaluronidase is an enzyme that hydrolyses hyaluronic acid, reducing its viscosity [Magistro, 1964]. Hyaluronidase carries a positive charge and migrates most rapidly at a pH of 5.4. For these reasons, it is applied in 0.1-mol/L solution with an acetate buffer by iontophoresis to an edematous limb [Popkin, 1951).

Vasodilators: Two potent vasodilators, histamine and mecholyl (acetyl-beta-methylcholine chloride) have been administered by iontophoresis for a variety of disorders. Kling and Sashin compared the efficacy of these two vasodilators and determined that mecholyl produced less vasodilation. They also used histamine iontophoresis for patients with a number of conditions, particularly arthritis. The authors reported reduced pain and increased range of motion. Because there was no change in joint swelling, it is possible that the improvements noted were largely due to pain modulation. Kling and Sashin also reported improvement in patients with conditions associated with vasospasm, such as Raynaud's disease (Yoshida and Roberts, 1992).

II. Conclusion

Iontophoresis is a means of applying pharmaceuticals to the organism based on physicochemical principles of attraction or repulsion of charges. Given the advantages observed in the use of iontophoresis such as transdermal topical application, its clinical and rehabilitative use is recommended. However, similar to other therapeutic modalities, its use should be preceded by a proper study of its possibilities and limitations. With research and development of new technologies, such as pharmaceuticals applied with microcapsules, the use of iontophoresis is more precise and controlled, increasing its treatment effectiveness. Currently the use in the field of physical therapy has a practical application and good results, especially since it is noninvasive and enables topical application of pharmaceuticals.

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