THE INTERNATIONAL JOURNAL OF SCIENCE & TECHNOLEDGE

Iontophoresis: A Non-Invasive Method of Propelling High Concentrations of a Charged Substance

Sameet Keshari Pati
2nd year Student, Departmeny of Mechanical Engineering
Gandhi Engineering College, Bhubaneswar, Odisha, India

Abstract:
The focus of this study is to review the latest developments and technologies on the field of medical science in penetrating chemical solutions through the skin.Formally, the modality can be defined thus: "a non-invasive method of propelling high concentrations of a charged substance, (normally a medication or bioactive agent), Trans dermally by repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber containing a similarly charged active agent and its vehicle". The term iontophoresis is simply defined as ion transfer (ionto = ion; phoresis = transfer). This includes new methodologies of insertion of chemical in to human body without any rupture in the peripheral in the receiver's body.Furthermore, the study looked into the reduction of transfusion prone diseases such as HIV etc. this also reduce the human fear and pain which is experienced during the process of injection of chemicals to the body. Nowadays the use of needles and injectors have effectively increases the cost of medicines which is available to commoners, so that this would be an alternative and this would be used again and again without and damage and neither would have an adverse effect on the being on which the chemical substance is used upon. Advancement on this will not only be an help to human kind but will be also an great achievement on medical science because after this it won't require an experienced hand to inject chemicals to an person.

Keywords: *Penetrating, non-invasive, Propelling, bioactive, repulsive, transfusion, peripheral, insertion*

Introduction

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". In the past it has sometimes been called Electromotive Drug Administration, though in modern therapy, this is a rarely employed term.This is not a new technique - there is recorded iontophoresis activity way back to the 1700's, though most authorities agree that it was not until the work of Le Duc in the early 1900's that the technique really gained momentum, though its use since that time has been sporadic.Iontophoresis is used in therapy, but is not exclusive to this arena, and there are applications in medicine, dentistry, lab sciences and physiology. A literature search will quickly identify thousands of references, though only a relatively small proportion of them will be directly relevant to therapy type applications. There have been several reviews over the years (see references at the end of this material) which will assist those with an interest in following up on the key literature. There are relatively few practitioners using iontophoresis in the UK, but in the USA it is a mainstream application. In Europe there are pockets of activity, and strong support from many practitioners. The use of iontophoresis worldwide is patchy - with areas of high use and areas where it is almost never employed.IONTOPHORESIS is NOT the same as PHONOPHORESIS which involves driving ions across the skin with therapeutic ultrasound. Bolin and Goforth, [1] has said in his journal of rehabilitation that electrical delivery can be easily tolerated by patients rather than any of the usual techniques of injecting and has said that it can be an effective substitute in the field of medical science and has described about its uses for rehab clinician. Gangarosa, L. P. et al, [2], has given about the enhancement for penetration of chemical and medicinal substance in to an individual's body. He has also shown that it can be effectively used for penetration of antiviral drugs and that too in an faster and effective rate which can serve as a greater help to mankind. Kalia, Y. N. et al, [3] has given an review report about the delivery of the drug by this process and by his review it can be considerably said that this process has not come up with any kind of disadvantages and defects so that it can be said as an affective substitute to the use of needle in the injections. Rothstein, J. M. et al. [4] has given an specialist review on this technique of iontophoresis and has suggested it uses in various field of medical science and has confirmed that use of electrical equipments in this process don't have any fearful results to the being and can be used with ease. Warden, G. D. [5] has given in his paper about the safety measures that should be taken while implementing this process and has given an acute detail on rehabilitation in his paper. He in his paper has mentioned about the implementation, working and has said the ways and methods make this method an effective one. Viscusi and Witkowski [13] has said iontophoresis as one of the best alternative method for drug delivery and

have given their brief idea on reducing the pain medicines so that to make the process more friendly and effective. Harris and Bertolucci[7,10] has said that iontophoresis can also be used in inflammatory conditions in musculoskeletal system and can be very much effective and would be very helpful in sports. Anderson ,Morris, Boeh[8] has given the magnitude of iontophoresis current on the body and has also given a brief description about the time limit for the exposure of that particular electric charge so that to reduce any kind of skin damage or radiation effect on the skin. Artusi, Nicoli, Colombo, Bettini, Sacchi, Sanli, Chou, Cheng, Yen, Jiang [9,11] has given an paper on pharmacy in which they have clearly mentioned about the uses and advantage of the iontophoretic deviece and has suggested that use of this type of products should be increased in medical science. Banga, Chien[12] has said that by this process of iontophoresis we can get an controlled release on the drug so that it could be planned and be done in an perfect manner.

1. Basic Principles

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, INACTIVE or RETURN electrode. For consistency in this document the terms ACTIVE and INDIFFERENT electrodes will be used.

1.1 IONIC PENETRATION

It is usually considered that the penetration of the ions into the tissues is likely to be less than 1mm. Any deeper penetration is considered to be due to local capillary circulation effects. There is no evidence that the current itself is responsible for penetrations beyond this level (though some authors claim - without explicit evidence - that the ions are driven much further into the tissues. The bulk of the ions that enter the tissues accumulate under the stimulating electrode and it may be possible that recombination of the substance can occur under this (active) electrode, though this remains a controversial issue which has not been fully resolved by the available research evidence.

It is possible that different ions will travel varying distances into the tissues - in other words, there is not a 'set' penetration which is equal for all different substances. This issue has also yet to be fully resolved.

1.2 Acid / Alkaline Reactions

Will get ACID accumulation under the POSITIVE (anode) electrode (weak HYDROCHLORIC ACID) because the negatively charged chloride ions (Cl- from NaCl) will transit (be attracted) towards the anode. Will get ALKALINE accumulation under the NEGATIVE (cathode) electrode (SODIUM HYDROXIDE) because the positively charged sodium ions (Na+ from NaCl) will move towards the cathode. The Na+ ionsreact with water to form sodium hydroxide (NaOH). N.B. it is suggested that the reaction at the negative (cathode) electrode will bring about a softening of the skin, hence is growing use by beauty therapy clinics.A reactive hyperaemia will be observable under BOTH electrodes due to (chemically mediated) local vasodilation. The magnitude of the local reaction (independent of the ions utilised) will depend on:

Current Intensity (more current, greater reaction)

Time (longer time, stronger reaction)

Tissue Resistance (greater resistance, stronger reaction)

The evidence is summarised by Belanger (2010) who concludes that based on the available evidence (e.g. Banga et al, 1998 and Anderson et al, 2003) the penetration of the ions is greatest in the region of the pores, the penetration of the substance through the skin is in proportion to the current magnitude, but that the substance is most likely deposited below the stratum corneum, thus acting as a depot. Onward migration of the substance to the deeper tissues is achieved by diffusion rather than being 'driven' deeper by the applied current.

Interestingly, it is also suggested that if there is a strong vasodilation in the blood vessels of the skin, there will be a less effective diffusion to the deeper tissues on the basis that the increased local flow will serve to dilute the sub epidermal deposit.

1.3 Polarity, Current Intensity and Drug Concentrations

There are some authors who identify very specific substance concentrations, volumes, electrode sizes, current intensity and treatment duration (the critical parameters for an iontophoresis treatment). Others provide general guidance, saying that it is not possible to be specific for a particular patients with a particular clinical presentation. In general terms, low current intensities appear to achieve favourable results. The treatment is usually applied with currents up to 5mA and with low ionic concentrations – up to 5%, though there are certainly reports and treatment suggestions that take the current intensity up to higher levels and employ 'stronger' substance concentrations. Treatment times are typically in the 20 - 40 minute range. There is evidence to suggest that using a higher concentration of the substance does not serve to increase the effectiveness of the therapy, and does not increase

the amount of the drug delivered to the tissues - low concentrations of drug (or substance) (typically 2-5%) and a low current intensity (up to 5mA) appears to be the most effective delivery method. It has been suggested that commonly, the NEGATIVE electrode is made larger (relative to the positive electrode) to avoid skin irritation (whether the ionic driving electrode or not). Figures often cited suggest that the negative (cathode) electrode should be 2 x larger than the positive (anode) electrode.

1.4 General Principles of Application:

It is preferable to utilise a direct current stimulator, commonly a dedicated iontophoresis device, or the DC/Iontophoresis output on a multi-modal machine.

1.4.1 Constant current

It is preferable to constant voltage - thus, whatever changes occur in terms of skin resistance, the magnitude of the applied current will not exceed the present level. Some machines offer you and a choice - and if that is the case, constant current will give you an effective and the safest application (smaller risk of skin burn).

1.4.2 Constant voltage

Stimulation can result in a burn more easily (in this case, the voltage is set by the operator. If the skin resistance changes, the current flow through the tissues will vary - and thus give rise to an increased risk of burn).

1.5 Preparation and Delivery

The skin should be abrasion / cut free and the area carefully washed (soap & water is fine). Some authorities have advocated the application of heat prior to the iontophoresis, but the experimental evidence does not support this. In fact, it appears to reduce the amount of drug passing through the epidermis and as identified in a previous section, increasing blood flow through the skin and superficial tissues may simply serve to reduce the size of the 'depot' in the skin. Ensure that all electrode pads are thoroughly soaked in either tap water or other appropriate solution prior to application. Dry electrodes are inappropriate and should not be used. If propelled electrodes are being used, ensure that a good even contact is achieved. Adequate fixation of the electrode and pad to the skin needs to be carefully maintained. Uneven current distribution can easily lead to skin burns and/or irritation Explain to the patient what is expected and ensure that they know to report immediately if any untoward or painful sensations are felt.
Turn the current up slowly to the required amountat the end of the treatment time, ensure that the current is turned down slowly.

2. Tables

2.1 Anodal and Cathodal Reactions in response to Iontophoresis [8]

Cathode	**Anode**
NEGATIVE electrode	**POSITIVE electrode**
Attraction of +ve ions	**Attraction of -ve ions**
Alkaline reaction by the formation of NaOH	**Acid reaction by the formation of HCl**
Increased density of proteins	**Decreased density of proteins**
Increased nerve excitability via a depolarisation effect	**Decreased nerve excitability via a hyperpolarisation effect (sometimes called anode blockade)**

2.2 Optimal Current Variables used in Iontophoresis [6]

Current Type	DC
Current Amplitude	**1.0 - 4.0 mA**
Treatment Duration	**20 - 40 minutes**
Total Current delivered	**40-80mA/min**

2.3 Table of Commonly Used Medications and Solutions with Iontophoresis [6]

Drug / Solution	Main Indication(s)	Rationale	Parameters
Acetic Acid	Calcific tendinitis (myositis ossificans)	Acetate believed to increase solubility of calcium deposits in tendons (and other soft tissues)	2 - 5% aqueous solution NEGATIVE pole
Calcium chloride	Muscle spasm (also hypersensitive peripheral nerves)	Calcium thought to stabilise excitable membranes, appears to decrease excitability threshold in peripheral nerves and skeletal muscle	2% aqueous solution POSITIVE pole
Dexamethasone	Inflammation	(synthetic) anti inflammatory	4mg/mL aqueous solution negative pole
Hydrocortisone	Inflammation	Steroid based anti-inflammatory	0.5% ointment POSITIVE pole (Rothstein et al)
Hydrocortisone, prednisone	Inflammation	Steroid based anti inflammatory	NEGATIVE pole (Belanger)
Iodine	Adhesive capsulitis Other soft tissue adhesive presentations Infection (microbial)	Iodine acts as a broad spectrum antibiotic. Its actions in relation to adhesive presentations appear not to be fully understood	5 - 10% solution (some use ointment) NEGATIVE pole
Lidocaine	Soft tissue pain Inflammation	Local anaesthetic effects (blocks peripheral nerve activity). May stimulate healing	4 - 5% solution (ointment) POSITIVE pole
Magnesium sulphate (sulfate)	Muscle spasm Myositis	Thought that 'relaxing' effect is achieved by decreased excitability of muscle membrane and reduced activity at neuromuscular junction	2% aqueous solution (ointment) POSITIVE pole
Hyaluronidase	Oedema (local) Subacute and Chronic stages	Increases permeability in connective tissues thus allowing dispersion of accumulated fluid. Hydrolysation of hyaluronic acid	Delivered after reconstitution with 0.9% sodium chloride (Normasol) to give a 150µg/mL solution POSITIVE pole
Salicylates	Muscle and Joint pain Acute and Chronic	Mode of action akin to Asprin - analgesia and anti inflammatory. Inhibits synthesis of prostaglandins	2-3% sodium sallicylate solution OR 10% trolaminesallicylate ointment NEGATIVE pole
Tolazoline hydrochloride	Ulcers (open wounds)	Stimulates local blood flow Stimulates tissue healing (thought to be via inhibition of local vascular smooth muscle contraction)	2% aqueous solution POSITIVE pole
Zinc Oxide	Open wounds - ulcers Some dermatological conditions	Antiseptic effects related to the zinc. May stimulate healing	20% ointment POSITIVE pole

2.4 List of Drugs Investigated Recently for Iontophoretic Delivery [13]

Drug	Animal/ Membrane Model Used	Experimental Conditions	Results
Thiocolchicoside	Rabbit and human skin	*In vitro*: Glass-Franz type cell.	Enhanced flux of the drug over passive control.
Salbutamol	Non rate limiting artificial membrane	*In vitro*: Release of drug from a liquid crystalline vehicle was studied.	Enhanced flux from the vehicle.
Timolol maleate (TM)	Excised rat, rabbit, guinea pig, mouse and human skin	*In vitro*: Valia-Chien side by side diffusion cell. Studied effect of species.	Iontophoretic transport highest in human skin and lowest in rabbits.
Dextran sulphate	Full thickness pig skin or epi-dermis separated from human cadaver skin	*In vitro*: Valia-Chien cell; 500 V; Current- 0.5mA/cm^2; Time – 6 h.	Cumulative amount fluxed from cathode was approximately 300 times more over passive and from anode it was 15 times more.
Diclofenac	Guinea Pig skin	*In vitro*: Current- 0.2 and 0.5 mA/cm^2; Time- 6 h. Studied effect of current on drug delivery.	Full plasma concentration achieved in 1 h. Drug delivery was proportional to current (371± 141 µgm / lt at 0.5 mA/cm^2 and 132 ± 62 µ gm/ lt at 0.2 mA/ cm^2).

3. Illustrations, Diagrams And Photographs

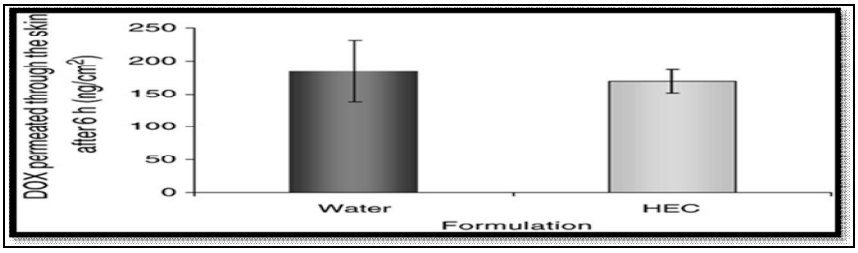

Fig 3.1. DOX passive permeation from these formulations showed that the drug does not cross the skin in quantifiable amounts after 6h. Therefore, iontophoresis facilitates DOX skin permeation.[8]

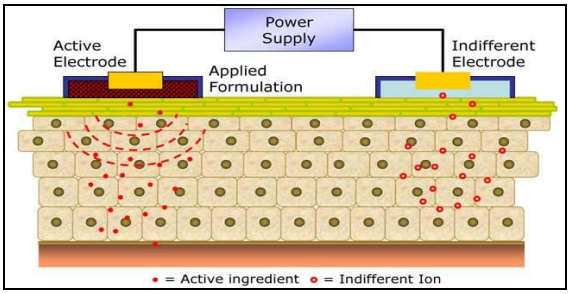

Fig 3.2. Ions with a polarity which is the same as that of the stimulating electrode are repelled into the skin [9]

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.

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, especially 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 discarded (they cannot be reused). The illustration of electrode systems (below) includes one such option (top right)

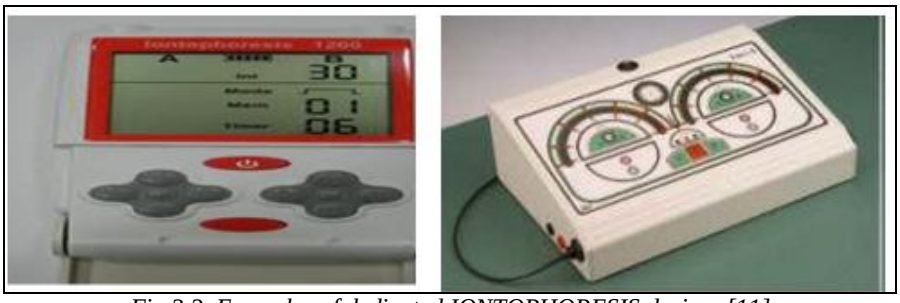

Fig 3.3. Examples of dedicated IONTOPHORESIS devices [11]

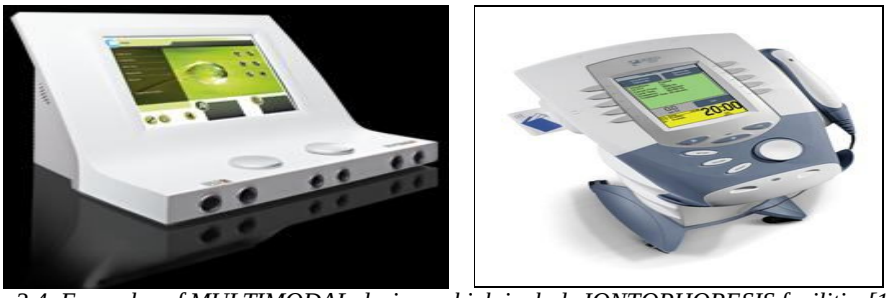

Fig 3.4. Examples of MULTIMODAL devices which include IONTOPHORESIS facilities[11]

4. Equations

4.1 Safe Current Density [5]

It is important to note that the current density (how strong the current is and also how concentrated it is), measured in mA/cm2, is an important factor in these treatments. If the current density reaches too high a level, tissue damage, and especially skin burn, may ensue.

It is suggested (see Belanger, 2010 for the full argument), that **a current density of no more than 0.5mA/cm2 is applicable at the negative (cathode) electrode and 1.0mA/cm2 at the positive (anodal) electrode**.

If a current of 2mA is delivered using an electrode of 6cm2, the current density will be 2(mA)/6(cm2) = 0.33mA/cm2, which is safe at either the positive (anode) or negative (cathode) electrode.

It is possible, using a transposition of the equation, to establish the maximal current that can be applied with a particular electrode whilst ensuring a safe treatment.

Maximum Current (mA) = Maximum Safe Current Density (mA/cm2) x Electrode area (cm2)

E.g.

If the (active) electrode to be used is 6cm2

If the active electrode is to be made NEGATIVE (cathode)

The maximum safe current density is 0.5mA/cm2

The maximum current that can be safely applied is therefore:

= 0.5mA/cm2) x 6 (cm2) = 3mA

5. References

1. Bolin, D. and M. Goforth, “Rehab Management: The Interdisciplinary Journal of Rehabilitation”(2004). "Electric delivery: generally well tolerated by patients, iontophoresis has many uses for the rehab clinician." Vol.17 (10), PP. 18-21.
2. Gangarosa, L. P. et al, “J Dermatol” (1995). "Iontophoresis for enhancing penetration of dermatologic and antiviral drugs." Vol.22 (11): PP. 865-875.
3. Kalia, Y. N. et al, “Adv Drug Deliv Rev” (2004). "Iontophoretic drug delivery.” vol.56 (5): PP.619-658.
4. Rothstein, J. M. et al , “The Rehabilitation Specialist's Handbook” (1998).. Philadelphia, F A Davis.
5. Warden, G. D.,“Rehab Management: The Interdisciplinary Journal of Rehabilitation” (2007). “Electrical safety in iontophoresis" Vol .20(2): PP 22-23.
6. Rothstein et al and Belanger, medication and solutions, (1998), vol 3(2), PP 45-56
7. Harris PR. “Iontophoresis: Clinical Research in Musculoskeletal Inflammatory Conditions.” J Ortho Sports PT. (1982);vol4: PP 109-112.
8. Anderson CR, Morris RL, Boeh SD, et al. “Effects of iontophoresis current magnitude and duration on dexamethasone deposition and localized drug retention.” PhysTher. (2003) ;vol 83: PP 161-171.
9. Artusi, M.; Nicoli, S.; Colombo, P.; Bettini, R.; Sacchi, A.; Sanli,P. J. Pharm. Sci. (2004), vol93 (10), PP 24-31.
10. Bertolucci, L.E. “Introduction of Anti-inflammatory Drugs by Iontophoresis: Double Blind Study.” J Orthopedic and Sports Physical Therapy. (1982); vol 4: PP 103-108

11. Chou, W.-L.; Cheng, C.-H.; Yen, S.-C.; Jiang, T.-S. Drug Dev. Ind. Pharm. (1996**)**, vol22(9&10), PP 43-50.
12. Banga, A.K.; Chien, Y.W. J. Control. Release, (1988), vol7(1), PP1-24.
13. Viscusi, E. R. and T. A. Witkowski, "Regional Anesthesia and Pain Medicine" (2005). "Iontophoresis: the process behind noninvasive drug delivery." Vol 30(3): PP 292-294