Available online on www.jadd.in

Journal of Advanced Drug Delivery 2014; 1(1); 58-70

ISSN: 2348-3792

Review Article

Iontophoresis: An Electrically Assisted Drug Delivery System

Tushar G, Rukari,*[1]Babita R. Alhat

1. VJSM'S Institute of Pharmacy, Ale.

Available online: February, 2014

Abstract:

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. New drug delivery system are also essential for the delivery of novel , genetically engineered pharmaceuticals (i.e. Peptides, Proteins) to their site of action, without incurring significant immunogenecity or biological inactivation. One of the methods most often utilized has been transdermal delivery meaning transport of therapeutic substances through the skin for systemic effect. Several new techniques have recently been developed which reduce the barrier properties of the stratum corneum and as a result significantly enhance the skin permeation of drugs. Iontophoresis is a process of transportation of ionic molecules into the tissues by passage of electric current through the electrolyte solution containing the ionic molecules using a suitable electrode polarity. Transdermal Iontophoresis should be called electrically assisted transdermal delivery.

Key Words: New drug delivery system, transdermal delivery, Iontophoresis, electrically assisted transdermal delivery etc.

INTRODUCTION:

Transdermal drug delivery system istopically administered medicaments in the form of patches that deliver drugs for systemic effects at a predetermined and controlled rate. A transdermal drug delivery device, which may be of an active or a passive design, is a device which provides an alternative route for administering medication. These devices allow for pharmaceuticals to be delivered across the skin barrier. In theory, transdermal patches work very simply.[1]A drug is applied in a relatively high dosage to the inside of a patch, which is worn on the skin for an extended period of time. Through a diffusion process, the drug enters the bloodstream directly through the skin. Since there is high concentration on the patch and low concentration in the blood, the drug will keep diffusing into the blood for a long period of time, maintaining the constant concentration of drug in the blood flow.[2]

CONDITIONS IN WHICH TRANSDERMAL PATCHES ARE USED:

Transdermal patch is used when:[3]

(1) When the patient has intolerable side effects (including constipation) and who is unable to take oral medication (dysphagia) and is requesting an alternative method of drug delivery.

(2) Where the pain control might be improved by reliable administration. This might be useful in patients with cognitive impairment or those who for other reasons are not able to self-medicate with their analgesia.

(3) It can be used in combination with other enhancement strategies to produce synergistic effects.

Conditions in which Transdermal Patches are not used:[4]

(1)Cure for acute pain is required.
(2) Where rapid dose titration is required.
(3) Where requirement of dose is equal to or less than 30 mg/24 hrs.

TRANSDERMAL DELIVERY: NEW APPROACHES:[5]

Several new techniques have recently been developed which reduce the barrier properties of the stratum corneum and as a result significantly enhance the skin permeation of drugs. Potential approaches used in overcoming the skin barrier properties are as follows:-

Physical Approaches

1. Iontophoresis.
2. Ultrasound.
3. Thermal Energy.
4. Stripping of Stratum Corneum.
5. Hydration of Stratum Corneum.

Chemical Approaches

1. Delipidisation of Stratum Corneum.
2. Synthesis of lipophilic analog.
3. Co-administration of cutaneous enzyme inhibitor.

Biochemical Approaches

1. Synthesis of bioconvertible prodrugs.
2. Co-administration of cutaneous enzyme inhibitor.

Mechanism of Action of Transdermal Patch:[6]

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

1. Iontophoresis
2. Electroporation
3. Application by ultrasound
4. Use of microscopic projection

IONTOPHORESIS:[7]

Different investigators have given different definitions because one simple definition cannot explain all the mechanisms involved. But for the sake of simplicity, "Iontophoresis is a process of transportation of ionic molecules into the tissues by passage of electric current through the electrolyte solution containing the ionic molecules using a suitable electrode polarity." This means it would involve an electromotive force. In the body, ions with a positive charge (+) are driven into the skin at the anode and those with negative charge (-) at the cathode. Iontophoresis is sometimes confused with electrophoresis and electro-osmosis, the former involving movement of the colloid (dispersed phase) and the latter involving the liquid (dispersion medium), which are quite different. Iontophoresis may however cause an increased transport of method of penetration of non-electrolytes through tissues (Figure 1).

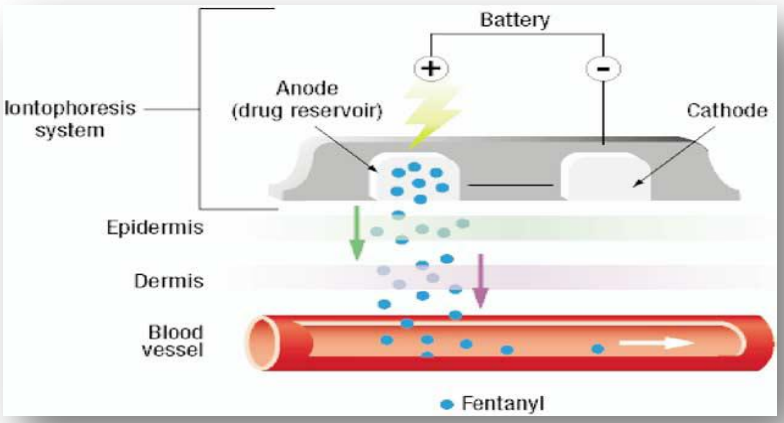


Figure 1. Iontophoresis- penetration of non-electrolytes through tissues

Iontophoresis Overview:

Iontophoresis is the method where the movements of ions across a membrane enhanced using an externally applied potential difference. When the membrane under consideration is skin, the method is called transdermal iontophoresis. The principle barrier to the transport of the molecules into an across the skin is stratum corneum (SC), this is the uppermost layer of the epidermis with a thickness of between 10-100 µm. The SC consists of several layers of corneocytes (a nucleate keratin filled cells) inlaid in a lipid matrix, a continuous medium through the SC, arranged mainly in bilayers.[8]The intercellular lipids consist of approximately equal quantities of ceramides, cholesterols and free fatty acids.Percutaneous absorption may take place simultaneously by any combination of the three main pathways that include; the intercellular (paracellular) pathway between the conneocytes along the lamellar lipids, the intracellular (transcellular) pathway through the cells or the appendageal (shunt) Pathway via hair follicles, sweat ducts and secretory glands.[9]

Ions prefer the routes of the least electrical resistance; in the SC this is believed to be via the pores. Some investigations indicate that these pores are sweat glands[10]others that transport occurs through both hair follicle and sweat glands.[11]The physicochemical properties of the molecules have an effect on the contribution of the follicular and non follicular routes of penetration. Hydrophilic molecules tend to localize in the hair follicles, whereas lipophilic molecules are mostly distributed in the lipid intercellular regions of the SC and the lipid membranes of the epidermal keratinocytes.[12]Since passive transdermal permeation of the majority of the drugs needs enhancement to achieve clinically relevant plasma concentrations, both chemical and physical enhancement methods have been developed. Iontophoresis is one of the physical methods.

In iontophoresis, cationic or neutral therapeutic agents are placed under an anode or anionic therapeutic agents under a cathode. When a low voltage and low current density is applied, according to simple electro repulsion, ions are repelled into and through the skin. Cationic drugs are driven into and through the skin by the anode (active electrode), which also extracts anion from the tissue underneath the skin

into the anode. At the cathode (return electrode) anionic buffer ions are driven into the skin and cations from the tissues are extracted into the cathode. It is also possible to include an additional charged drug in the return electrode to be delivered simultaneously or to use a mixture of drugs in the active electrode to enhance the desired effect or to increase skin permeation, depending on which drugs/molecules are used.[13,14]

More formally, transdermal iontophoresis should be called electrically assisted transdermal delivery. There are three major enhancing mechanisms for drug flux through the skin, of which iontophoresis (also known as electrorepulsion, or electromigration or the Nernst-Planck effect) is just one. The other mechanisms are electoroosmotic flowand current induced increase in skin permeation, also known as damage effect.[15-20]Electroosmotic flow is a flux or bulk fluid induced by a voltage difference across a charged membrane; it is always in the same direction as the flow of counter ions. Since human skin is negatively charged under physiological conditions, the counter ions are cations and the electroosmotic flow is thus from anode to cathode. Therefore, the cathodic delivery of anions is hindered and the anodic delivery of cations is assisted by electroosmosis.

The improved movement of neutral molecules under iontophoresis is based on electroosmosis. Ions are influenced by all of the above mechanisms so that electroosmosis has a positive contribution to the transport of cations and a negative contribution to the transport of anions under normal physiological conditions. The impact of electroosmosis on ion transfer increases with the size of the ion. [21]The contribution of electroosmosis can be so significant that the delivery of large anion from the anodic compartment can be more efficient than delivery from cathode, this is called wrong-way iontophoresis.[18] The electrorepulsion effect gives the largest enhancement to the flux of small lipophilic cations.[22] When the concentration of the ionic drug is very high, so that the drug carries most of the current, electroosmotic flow has a very small effect on the drug flux.[16]Transdermal iontophoresis has been used for both local and systemic drug delivery. Applications include local delivery of anaesthetics (e.g. lidocaine),[23]steroids and retinoids to treat acne scarring [24] for the relief of palmar and plantar hyperhidrosis,[25] and the administration of pilocarpine in the diagnosis of cystic fibrosis.[26-28]Other applications of transdermal iontophoresis include the administration of antiinflammatory drugs e.g. ketoprofen in to subcutaneous tissues and joints.[29]Iontophoretic delivery of several systemic drugs is still under investigation. These include the analgesic, fentanyl, [30]a reversible cholinesterase inhibitor, tacrine III and several formulations of insulin. The symmetrical nature of iontophoresis, where ions are driven both into and out of the body, has been utilized for extracting information from the body without the need for blood sampling.[21,31-34]

The method of iontophoresis was described by Pivati in 1747. Galvani and Vota two well known scientists working in the 18th century combined the knowledge that the electricity can move different metal ions and the movement of the ions produce electricity. The method of administering pharmacological agents by iontophoresis became popular at the beginning of 20th century due to the work of Leduc (1900) who introduced the term iontotherapy and formulated the laws for this process.[35]

CRITERIA FOR IONTOPHORESIS:

There are some very important rules that have to be followed when doing iontophoresis;[36]

1. The selected molecule must be ionised into positive and negative components and be maintained as ions during the treatment.
2. The size of the ion is important. For example even though a complex protein like collagen may be possible to ionise, the size of the important ion of collagen is so large that it cannot be transported through skin.
3. There is a limit to the number of polar substances that can be used simultaneously. We believe that during iontophoresis "pores" open up through membranes and the charged particles can move through them. If there are too many charged particles then the "pores" may be "blocked" by the crowd of ions converging all at once.
4. The ion must be water-soluble because electricity is only conducted through water and not lipids.
5. The pH of the active gel is of fundamental importance. The right ingredient at the right concentration won't work properly if the pH is wrong. Each ion has it's own ideal pH at which it will be ionised best.
6. The current used must be appropriate.
7. The current used should be high enough to be effective and still safe. The higher the current, the faster the ions will move.
8. Intermittent current works better than continuous current because as the ion moves into the skin it will react with other chemicals and needs to be re-ionised.
9. The treatment period should be at least 10 minutes and probably not longer than 30 minutes. Most of the ions pass through the skin at about 8 to 15 minutes and then relatively little passes through after 30 minutes.
10. It is possible, maybe even highly desirable to treat skin with only one polarity. It is not necessary to treat the skin with the opposite current after doing the active treatment.

Advantages:[37]

1. Topical patches are a painless, noninvasive way to deliver substances directly into the body.
2. Topical patches are a better way to deliver substances that are brokendown by the stomach acids, not well-absorbed from the gut, orextensively degraded by the liver.
3. Topical patches over a controlled, steady delivery of medication over longperiods of time.
4. Topical patches have fewer side effects than oral medications or supplements.
5. Topical patches are easier to use and remember.
6. Topical patches over an alternative to people who cannot, or prefer not to take medications or supplements orally.
7. Topical patches are cost-effective.
8. People prefer topical patches.
9. TDDS of many ionized drug at therapeutic levels was precluded by their slow rate of diffusion under a concentration graduation, but iontophoresis enhanced flux of ionic drugs across skin under electrical potential gradient.[38]
10. Permit a rapid termination of the modification, if needed, by simply by stopping drug input from the iontophoretic delivery system.[39]
11. 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, eg. Thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, inter ferons, enkaphaline, etc. [40]

12. A constant current iontophoretic system automatically adjust the magnitude of the electric potential across skin which is directly proportional to rate of drug delivery and therefore, intra and inter-subject variability in drug delivery rate is substantially reduced. Thus, minimize inter and intra-patient variation.[41]
13. Iontophoresis turned over control of local anesthesia delivery in reducing the pain of needle insertion for local anesthesia. [42]
14. Iontophoretic delivery prevents contamination of drugs reservoir for extended period of time.[43]
15. 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.[44]

Limitations:

1. Iontophoretic delivery is limited clinically to those applications for which a brief drug delivery period is adequate.[45]
2. An excessive current density usually results in pain. [45]
3. 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.[45]
4. Burns are caused by electrolyte changes within the tissues.[46]
5. The safe current density varies with the size of electrodes.[46]
6. High molecular weight 8000-12000 results in a very uncertain rate of delivery.[46]
7. The high current density and time of application would generate extreme pH, resulting in a chemical burn.[47]
8. Electric shocks may cause by high current density at the skin surface.[47]
9. Possibility of cardiac arrest due to excessive current passing through heart.[43]
10. Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.[43]

FACTORS INFLUENCING IONTOPHORETIC DRUG DELIVERY SYSTEM:

PHYSICO-CHEMICAL PARAMETERS: [47]

The movement of drug ions across the skin is dependent not only the magnitude of apparent electric field, but also upon the concentration of solution, the molecular size of drug to be passed, as well as charge and valence of ion.

pH:

The iontophoretic drug delivery rate is dependent on the ionic form of drug delivery, which is extremely effected by the pH of the system, when the skin is maintained at a negative charge by exposing the solution with pH 4 or higher, it facilitate the transdermal delivery of cationic drugs.

Species variation:

The wide differences in physical characteristics such as appendages per unit area, thickness and structural changes between human and laboratory rodent display a variation in penetration of drugs The average penetration of drugs is in order of rabbit > rat > guineas pig > human. Human skin is very much less permeable

than other rodents but iontophoretic delivery of drug is 7-fold greater in human skin consists of greater negative charge/or greater area fraction of negative pores.

Concentration:

The concentration dependent iontophoretic delivery has not been fully investigated, some of the authors reported that as the concentration of drugs viz. Hydromorphones and acetate ions increase in reservoir system then permeation of drug also increases. The iontopheric delivery of insulin does not effected by the reservoir concentration at the current range of 0.2 – 0.8 MA.

Buffer Systems:

Buffer systems also affect the permeation of drugs by iontophoresis. It is important to optimize the concentration of buffer species in the system and should be sufficiently high to maintain good buffer capacity but should not reach an extent such that the current is mostly carried by the buffer species instead of drug special which may result the low efficiency of iontophoretic permeation.

Ionic Strength:

The ionic strength of a drug delivery system is directly related to the iontophoretic permeation of drugs. Some authors reported that increasingly the ionic strength of the system decreases the permeation rate of and has no significant effect on penetration up to the 0.5.

Electrodes:

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

ELECTRICAL PARAMETERS:

The extent of charged molecules, which may penetrate through the skin, are theoretically proportional to the intensity of current and the duration of treatment for a transdermal iontophoretic delivery. The relationship between the drug delivery rate (D) and current (I) follows the given question:

$D = It M/Zf$

Where, t is the fraction of current carried by drug ions or transference number, M is the molecular weight of drug ion, Z is the molecular charge per drug ion and F is Faraday's constant.[49-50]

Voltage:

The ionic flux due to an applied voltage drop across a membrane is based on the fundamental thermodynamic properties of the system. The diffusion of drug during iontophoresis follows Nernst-Plank equation. It states that the flux of the ionic drug due to applied electric filed is directly proportional to the voltage drop and charge of the ion. The enhancement factor for hairless mouse skin showed good agreement up to 0.5 volts and significantly higher at 1.0 volt due to skin damage but it is up to 0.25 V.[51]

Resistance:

The electrical resistance of the skin varies widely with iontophoretic drug delivery. The resistance of the skin during iontophoretic application was much lower on sweat pores, especially when they discharge sweat. A slight fall in resistance occurs when electrode was interested in to the epidermis.[52]

Frequency/Impedance:

The frequency of the applied current charges especially in man, variability of frequency dependent impedance of human skin ranges from 10 KHzs
to 100 Khzs. The impedance of the skin decreases at higher frequencies less time is available to accumulate the charge on the skin surface during an applied pulse. The iontophoretic delivery of insulin decreases with increasing the frequency in the range of 50-2000 Hzs. The theoretical relationship between impedance of skin and frequency follows this equation:[49,53]

$1/ZT = 1/ZR + 1/ZC$

On/Off Ratio:

The on/off ratio of electricity effects the relative proportion of polarization and depolarization of skin, which results the efficiency of transdermal iontophoretic drug delivery. The number of on/off cycles in each second is shown as frequency. For example the on/off ration 1:1 at frequency 2000 Hzs (0.5 ms/cycle) provides 0.25 ms depolarization period and same time for the polarization.[49,53]

OPERATIONAL PARAMETERS:

The transport of drug delivery depends on the duration of current applied in iontophoretic drug delivery.[56]The iontophoretic penetration of drug linearly increased with increasing application time. [58] 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.[31]

Mode of Current:

Direct current (DC) iontophoretic dosing of drug inevitably develops a skin polarization potential, which reduce the efficiency of iontophoretic delivery and cause skin irritation, burning and redness. But pulsed DC dosing pattern is effective for drug transport, the same time average voltage because it faces lower skin resistance in comparison to simple DC application in flux enhancement.[53]

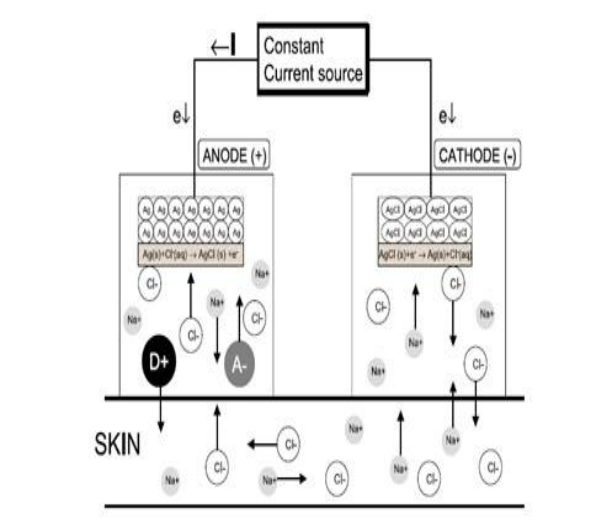
IONTOPHORETIC DEVICES:[7]

The main manufacturing concerns as in any equipment should include safety, convenience, reliability and reproducibility of the device. The iontophoretic device mainly consists of two parts components of the equipment are:

a. Electrical Circuit.
b. Electrodes.
    1. DC power supply
    2. A milliammeter
    3. A timer
    4. A rheostat
    5. The 2 electrodes +ve and –ve.

An iontophoretic device comprises a power source and two electrode compartments. The drug formulation (D^+A^-) containing the ionized molecule (D^+) is placed in the electrode compartment bearing the same charge; for example, a positively charged drug such as lidocaine would be placed in the anodal compartment. The indifferent electrode compartment is placed at a distal site on the skin. Once the current is applied, the electric field imposes a directionality on the movements of the ions present: positive charges in the anodal compartment move towards the cathode whereas anions move in the opposite direction. The electrochemistry occurring at the Ag anode necessitates the presence of Cl^- ions in the anodal compartment: this requirement usually leads to a decrease in drug delivery efficiency since the NaCl commonly used to provide Cl^- also introduces significant concentrations of highly mobile Na^+ ions which compete

very effectively with the drug to carry current. As the Cl^- ions arrive at the electrode– solution interface, they react with the metallic silver to form silver chloride, which on account of its low solubility product, is deposited at the electrode surface, simultaneously releasing an electron. In order to maintain electroneutrality in the anodal compartment, either a cation must move out of the compartment and into the skin or an anion must leave the skin and move into the anodal chamber. In the cathodal compartment, the AgCl is reduced by the arrival of electrons from the power supply and yields metallic silver together with a Cl^- ion, which passes into the solution. Again, for electroneutrality, this must be compensated for by the arrival of a cation from within the skin into the cathodal chamber or by the loss of an anion. Since the electrical circuit is completed by the endogenous inorganic ions that are present in the skin, primarily Na^+ and Cl^-, these latter species can impact on the efficiency of drug transport (Figure 2).[55-58]



BIOMEDICAL APPLICATION:

Iontophoresis has wide applications in Dermatology, Ophthalmology, ENT, Allergic conditions even in Cardiac and Neurological situations, but its greatest advantage is in the transport of protein or peptide drugs which are very difficult to transport trasdermally due to their hydrophilicity and large molecular size.[9]

CONTRAINDICATIONS FOR IONTOPHORESIS:

Contraindications for iontophoresis are important in patients with higher susceptibility to applied currents. Such patients include those carrying electrically-sensitive implanted devices such as cardiac pacemakers, those who are hypersensitive to the drug to be applied, or those with broken or damaged skin surfaces.[59]

REFERENCE:

1. Ansel HC, Loyd AV, Popovich NG. Pharmaceutical dosage forms and drug delivery systems. Seventh edition. Philadelphia: Lippincott Williams and Willkins publication; 1999.
2. Brahmankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics A Teatise, Vallabh Prakashan,Delhi, 1995.
3. Guy, Richard H, Hadgraft, Jonathan.,Transdermal Drug Delivery. Second Edition, Informa Health Care, 2002.
4. Arcangelo , Virginia P, Peterson, Andrew M, Pharmacotherapeutics for Advanced Practice,3rd Edition, Lippincott Williams and Willkins publication, Philadelphia, 2005.
5. Vyas SP, Theory and Practice In Novel Drug Delivery System,1stEdition,CBS Publications, New Delhi,2009.
6. Shah S. Transdermal Drug Delivery Technology Revisited: Recent Advances [Online]. 2008 [Cited 2013 Aug

7].Available from URL: http://www.pharmainfo.net/reviews/transdermal-drug-delivery-technology-revisited-recent-advances

7. Korula M. Iontophoretic delivery of drugs [Onlone]. 2004[Cited 2013 Aug 7]. Available from URL: http://www.theiaforum.org/Article_Folder/iontophoretic-delivery-of-drugs.pdf.
8. Bouwstra JA, De Vries MA, Gooris GS, Bras W, Brussee J, Ponec M, Thermodynamic and structural aspects of the skin barrier, J Control Release1991, 15:209-20.
9. Schnetz E, Fartasch M, Microdialysis for the evaluation of penetration through the human skin barrier: A promising tool for future research, Eur J Pharm Sci, 1991, 12:165-74.
10. Abramson HA, Gorin HH. Skin reactions, IX the electrophoretic demonstration of the patient pores of the living human skin, its relation to the charge of the skin, J Phys Chem 1940, 44:1094-102.
11. Del Terzo S, Bhel CR, Nash RA, Iontophoretic transport of a homologues series of ionized and non-ionized model compounds, Influence of Hydrophobicity and mechanistric interpretation, Pharm Res, 1989, 6:85-90.
12. Turner NG, Guy R. Iontophoretic transport pathways, dependence on penetrant physiochemical properties, J Pharm Sci, 1997, 86: 1385-9.
13. Deagle WR, inventor; Iontophoresis dis pain blocker, U.S. patient No. US2003100884. 2003 May 29.
14. Riviere JE, Monteiro NA, Inman AO, Determination of lidocaine concentrations in skin after transdermal iontophoresis: Effects of vasoactive drugs, Pharm Res,1992, 9: 211-4.
15. Pikal MJ, Shah S, Transport mechanisms in iontophoresis II. Electroosmotic flow and transference number measurement for hairless mouse skin. Pharm Res,1990, 7: 313-21.
16. Pikal MJ, Transport mechanisms in iontophoresis-I, A theoretical model for the effect of electroosmotic flow on flux enhancement in transdermal iontophoresis, Pharm Res, 1990, 7: 118-26.
17. Pikal MJ, The role of electroosmosic flow in transdermal iontophoresis, Adv Drug Del Rev, 1992, 9: 201-37.
18. Pikal MJ, The role of electroosmosic flow in transdermal iontophoresis, Adv Drug Del Rev, 2001, 46: 281-305.
19. Uitto OD, White S, Electrosmotic pore transport in human skin. Pharm Res, 2003, 20: 646-52.
20. Inada H, Ghanem AH, Higuchi WI, Studies on the effects of applied voltage and duration on human epidermal membrane alteration/recovery and the resultant effects upon iontophoresis. Pharm Res. 1994, 11: 687-97.
21. Pillai O, Borkute SD, Sivaprasad N, Panchagnula R. Transdermal iontophoresis of insulin II: Physiochemical considerations. Int J Pharm, 2003, 254: 271-80.
22. Marro D, Kalia YN, Delgado-Charro MB, Guy R, Contributions of electromigration and electroosmosis to iontophoretic drug delivery. Pharm Res,2001, 18: 1701-8.
23. Maloney JM. Local anesthesia obtained via iontophoresis as an aid to shave biopsy, Arch Dermatol. 1992,128: 331-3.
24. Schmidt JM, Binder M, Maicheiner W, Bielglmayer C, New treatment of

atrophic acne scars by iontophoresis with estriol and tretinoin. Int J Dermatol, 1995, 34: 53-7.

25. Sloan JB, Soltani K. Iontophoresis in dermatology, J Am Acard Dermatol,1986,5: 671-84.
26. Gibson LE, Cooke RE, A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis, Pediatrics, 1959, 23: 545-9.
27. Gibson LE, Iontophorestic sweat test for cyctic fibrosis, technical details, Pediatrics 1967, 39: 465-9.
28. Webster HL, Barlow WK, New approach to cystic fibrosis diagnosis by use of an improved sweat-induction/collection system and osmometry, Clin Chem,1981, 27: 385-7.
29. Panus PC, Campbell J, Kulkarni SB, Herrick R, Ravis WR, Banga AK, Transdermal iontophoretic delivery of ketoprofen through human cadaver skin and in humans, J Control Release,1997, 44: 113-21.
30. Ashburn MA, Streisand J, Zhang J et al, The iontophoresis of fentanyl citrate in humans. Anesthesiology,1995, 82: 1146-53.
31. Chein YW, Siddique O, Shi WM, Lelawongs P, Liu JC, Direct current iontophoretic transdernal delivery of peptide and protein drugs, J Pharm Sci,1989, 78: 376-83.
32. Stepen RL, Petelenz TJ, Jacobsen SC. Potential novel methods for insulin administration: Iontophoresis. Biomed Biochem Acta, 1984, 43: 553-8.
33. Pillai O, Nair V, Panchagnula R, Transdermal iontophoresis of insulin IV: Influence of chemical enhancers. Int J Pharm,2004, 269: 109-20.
34. Rastogi SK, Singh J, Transepidermal transport enhancement of insulin by lipid extraction and iontophoresis, Pharm Res, 2002, 19: 427-33.
35. Rawat S, Vengurlekar S, B Rakesh, Jain S, Srikarti G, Transdermal delivery by iontophoresis,2008, 4: 1-1
36. Fernandes D. Treating Damaged Skin [online]. 2000 [Cited 2013 Aug 7]. Available from URL: http://www.dermaconcepts.com/documents/0000/0072/Treating_Damaged_Skin.pdf.
37. Baheti SR, Wadher KJ, Umekar MJ,A recent approach towards Transdermal Drug delivery by Physical and Chemical Techniques,Internationale Pharmaceuticasciencia,2011, 1(1): 42-53.
38. Srinivasan V, Higuchi WI, Ghenem AH, Behl CR, Transdermal Iontophoric drug delivery: mechanistic analysis and application to polypeptide delivery, J Pharm Sci, 1989, 78: 370-375.
39. Bodde HE, Verhoef JC, Ponec M,Transdermal peptide delivery,Biochem Soc Trans, 1989, 17(5): 943-5.
40. Phipps JB, Padmanabhan RV, Lattin GA, Iontophoretic Delivery of model inorganic and drug ions, J Pharm Sci,1989, 78: 365-69.
41. Kalia YN, Naik A, Garrison J, Guy RH,Iontophoretic drug delivery, Adv Drug Deliv Rev 2004, 56: 619–58.
42. Zetzer L, Regalado M, Nichter LS, Barton D, Jennings S, Pitt L,Iontophoresis versus subcutaneous: a comparison of two methods of local anesthesia delivery in children, Pain 1991, 44: 73-78.

43. Phipps JB, Padmanabhan RV, Lattin GA, Iontophoretic delivery of model inorganic and drug ions, J Pharm Sci, 1989, 78: 365-369.
44. Zakzewski CA, Li JK,Pulsed mode constant current iontophoretic transdermal metoprolol tartrate delivery in established acute hypertensive rabbits, J Control Release,1991, 17: 157-62.
45. Sanderson JE, Riel SD, Dixon R, Iontophoretic delivery of non-peptide drugs: Formulation optimization for maximum skin permeability,J Pharm Sci, 1989, 78(5):361-64.
46. Moliton H, Fernandez L,Experimental studies on the causes and prevention of iontophoretic burns, Am J Med Sci, 1939, 198(6):778-84.
47. Madhulatha AVS, Himabindu AVS, Ravikiran TN,Iontophoresis: A Newer Technology, International Journal of Research in Pharmaceutical and Nano Sciences,2012, 1(2): 190- 201.
48. D'Emanuele A, Staniforth JN,An electrically modulated drug delivery device II, Effect of ionic strength, drug concentration and temperature, Pharm Res,1992, 9(2): 215-19.
49. Liu JC, Sun Y, Siddique O, Chien YW, Shi WM, Li J, Blood glucose control in diabetic rats by transdermal iontophoric delivery of Insulin, Int J Pharm, 1988, 44: 197-04.
50. Murthy NS, Zhao YL, Hui SW, Sen A, Electroporation and transcutaneous extraction (ETE) for pharmacokinetics studies of drugs, J Control Release,2005, 105: 132-41.
51. Schultz SG, Basic Principles of Membrane Transport,Cambridge University Press, New York,
52. 1980.ShindeAJ, Shinde AL, Garala KC, Kandekar SA, More HN, Physical Penetration Enhancement By Iontophoresis: A Review, Int J Curr Pharm Res,2010, 2(1): 1-9.
53. Nandy BC, Mazumder B, SandipanR et al, Transdermal Electronically Assisted Technologies: Current Approaches on Iontophoretic Delivery System; International Journal of Drug Formulation And Research, 2011, 2(4),1-31.
54. Abramowitz D, Neoussikine B, Treatment by Ion Transfer, Grune and Stratton, New York,1946.
55. Lelawongs P, Liu JC, Chien YW,Transdermal iontophoretic delivery (II): Evaluation of electrical and operational factors, Int J Pharm, 1990, 61, 179.
56. Cullander C, What are the pathways of iontophoretic current flow through mammalian skin? Adv Drug Del Rev,1992, 9: 119-35.
57. Phipps JB, Padmanabhan RV, Lattin GA, Iontophoretic Delivery of model inorganic and drug ions, J Pharm Sci, 1989, 78: 365-69.
58. Sage BH, Riviere JE, Model Systems in Iontophoresis- Transport efficacy, Adv Drug Deliv Rev,1992, 9: 265-87.
59. Gazelius B,Iontophoretic-Theory, Innovations in Microvascular Diagnosis,1999; 7: 1-9.