IJPSR (2015), Vol. 6, Issue 8 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 31 December, 2014; received in revised form, 12 March, 2015; accepted, 15 July, 2015; published 01 August, 2015

IONTOPHORESIS: CONTROLLED TRANSDERMAL DRUG DELIVERY SYSTEM

N. Kirubakaran *[1], M. Chandrika [1] and K. Reeta Vijaya Rani [2]

Himalaya Drug Company[1], Makali, Bangalore, Karnataka, India
Periyar College of Pharmaceutical Sciences [2], Trichy, Tamil Nadu, India

Keywords:

Controlled, Transdermal, Iontophoresis, Ionicmovement, Skinpenetration, Electro osmosis

Correspondence to Author:
N. Kirubakaran

Research Associate
Himalaya Drug Company,
Makali, Tumkur Road,
Bangalore-562123, Karnataka, India.

E-mail: kirubakaran_14@yahoo.co.in

ABSTRACT: Currently there has been an increased interest in using iontophoretic technique for the controlled transdermal drug delivery of medicines, especially in the delivery of proteins & peptides through skin membranes. The delivery of ionic drug molecules and peptide/protein molecules through transdermal delivery to attain a systemic therapeutic effect, chemical or physical methods are needed to improve the rate of penetration of therapeutic drug molecule through the main diffusion barrier present in the skin membrane. In that, the iontophoretic technique is one of the most desirable to enhance the transdermal drug delivery of high molecular weight substances like peptide and proteins using a lower current intensity with a short time period for the desired therapeutic effect. This article is an complete overview of the controlled transdermal drug delivery of ions/proteins/peptides by iontophoresis as well as the principles, laws, mechanisms, factors, design considerations, applications, advantages, limitations of transdermal iontophoretic drug delivery system.

INTRODUCTION: There has been a huge awareness in recent years of potential therapeutic importance of achieving true controlled drug delivery manner where the release rate of drug output may be modulated in a precisely controlled, predictable manner. Transdermal iontophoretic drug delivery system has one of the useful techniques in achieving the controlled delivery of pharmaceuticals, especially which drug molecules are relatively small in molecular size and rather lipophilic in nature.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(8).3174-85

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(8).3174-85

However, these systems are rather limited in their capability of achieving the transdermal delivery of high molecular weight substances like peptides, proteins and oligonucluoside drug molecules which is often charged and high range of hydrophilic in nature. In order to overcome the delivery of ionic drug molecules and peptide/protein molecules through transdermal delivery to attain a systemic therapeutic effect, chemical or physical methods are needed to improve the rate of penetration of therapeutic drug molecule through the main diffusion barrier present in the skin membrane.

In that, the iontophoretic technique is one of the most desirable to enhance the transdermal drug delivery of high molecular weight substances like peptide and proteins using a lower current intensity with a short time period.[1]

Transdermal Drug Delivery System:

The advantages of using transdermal drug delivery system include improved systemic bioavailability and also reduce the hepatic metabolism. Various parameters in oral administration such as pH, the presence of food or enzymes and the gastrointestinal transit times can also be eliminated in current development of new transdermal drug delivery devices.

The aim is to obtain controlled, predictable and reproducible release of drugs into the blood stream of the patient for the treatment of disease conditions. The transdermal delivery device acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug delivery flux is controlled by the transdermal device instead of the skin, the inter and intra subject variation is smaller due to the drug release from the device can be controlled accurately by the transdermal device than the permeability of the skin.

Recently it is evident that the advantages of intravenous drug infusion can be duplicated, without its hazards and side effects by using the skin as the port of drug administration to provide continuous transdermal drug infusion in to the systemic blood circulation for the effective therapeutic range for the treatment of diseases. The drug penetration across epithelial borders is a slow process due to the effect of barrier properties. The skin, in particular, the stratum corneum, possesses one of the barriers to drug penetration due to its high level density (1.4/cm^2in dry state) and its low hydration of 10% to 20%. The barrier function is further facilitated by the continuous replacement of stratum corneum with various methods like penetration enhancers, physical methods etc.[2]

Advantages of Transdermal Drug Delivery System:

1. Easy and painless
2. Protects the active compound from gastric enzymes
3. Avoids the hepatic first-pass effect
4. Controls absorption rate [3]
5. Avoid drug interference due to the presence of food in intestinal tract
6. Avoids the variations in drug delivery rates
7. Minimize the patient compliance
8. Suitable method for unconscious patients
9. Possibility of fast termination of drug delivery from the device patch when if needed conditions[4]

Iontophoretic Drug Delivery System:

The iontophoretic drug delivery method was described by Pivati in the year of 1747. The two well-known scientists named Galvani and Vota working in the 18th century and they are combined the knowledge that the electricity can move different metal ions and the movement of the ions causes the electricity. At the begin of 20th century, the method of administering pharmacological agents by iontophoresis drug delivery became popular due to the work of Leduc(1900) who introduced the technical term iontotheraphy and he formulated the laws for this iontophoretic process drug delivery system.[4]

Definition of Iontophoresis:

The term iontophoresis is defined as the introduction by means of a direct electrical current of ions of soluble salts form of drug into the tissue or the body for therapeutic purposes. It is the novel technique used to increase the absorption of drugs across biological tissues such as the skin membrane.[5]

An Overview of Iontophoresis Technique:

Iontophoresis drug delivery system is the method, where the movements of ions across a membrane enhanced by using an externally applied potential current difference. When the membrane used skin is defined as transdermal iontophoresis.

The main principle barrier to the transport of the drug molecules across the skin membrane is stratum corneum (sc). The stratum corneum is the uppermost layer of the epidermis part with a thickness range of 10-100µm.[4]

Classification of Iontophoresis:

1. Transdermal iontophoresis
2. Ophthalmic iontophoresis
3. Transungual iontophoresis
4. Buccal iontophoresis
5. Ural iontophoresis
6. Trans nasal iontophoresis

Transdermal Iontophoresis:

Defintion of transdermal iontophoresis:

Recently there has been an increased interest in using iontophoretic technique for the transdermal drug delivery of medications both ionic and non-ionic drug molecules like peptides and proteins etc.,Iontophoresis is the method where the movement of ions across a membrane enhanced using an externally applied potential difference. When the membrane under consideration is skin, the method is referred as "transdermal iontophoresis"

Transdermal skin penetration mechanism:

The percutaneous drug absorption take place by any combined effect of the three pathways like intercellular(paracellular) pathway between the conneocytes along the lamellar lipids, the intracellular(trans cellular)pathway through the cells or the appendageal (shunt) pathway by hair follicles, sweat ducts and the secretary glands. Iniontophoresis, the ions prefer the routes of the least electrical resistance (I) in the stratum corneum this is event to be by the pores present in the skin. Some investigations point out that these pores are like sweat glands and also the transport occurs via both hair follicle and sweat glands.[4]

The physical and chemical natures of the drug molecules also have an effect on the contribution of the follicular and non-follicular pathways of drug penetration. Hydrophilic drug molecules tend to localize in the hair follicles, whereas the lipophilic drug molecules are mostly penetrated in the lipid intercellular regions of the stratum corneum and the lipid membrane part of the epidermal keratinocytes in the skin. Since the passive transdermal system of majority of the drug molecules necessary enhancement to attained the clinically relevant plasma drug concentrations for the therapeutic purposes. This is possible by the physical and chemical enhancement methods.[4]

Mechanism in Iontophoretic Drug Delivery System:

Electrical circuit pathway:

In the iontophoretic drug delivery system, the cationic or neutral drug molecules are placed in an anode chamber and anionic drug molecules placed in cathode. When a low voltage of low current density is applied, according to simple electro repulsion, ionic drug molecules are repelled into and through the skin membrane. In that the cationic drug molecules are driven into and through the skin membrane by the anode (active electrode), also which extracts anion from the tissue underneath the skin into the anode. At the same time the cathode (return electrode) anionic buffer ion molecules are driven into the skin membrane and the cation molecules from the tissues are extracted into the cathode.[4] (**Fig. 1**)

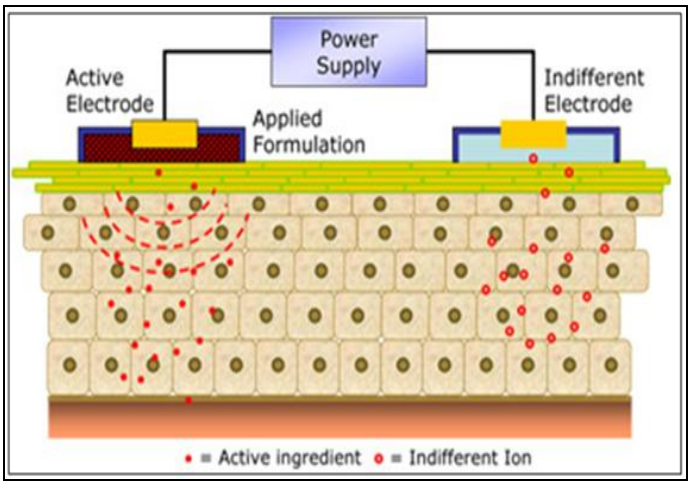

FIG.1: MECHANISM OF IONTOPHORETIC DRUG DELIVERY SYSTEM

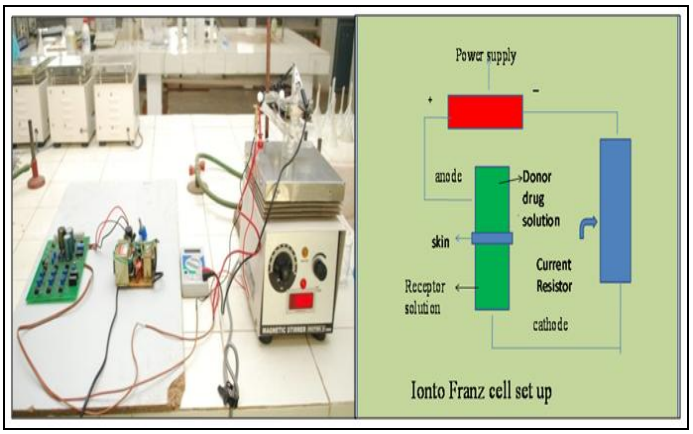

FIG.2: MECHANISM OF IONTOPHORETIC DRUG DELIVERY SYSTEM

Skin pathway:

Skin is known to consists of lipids (15-20%) (Triglycerides, free fatty acids, cholesterol and phospholipids), 40% proteins (mostly keratin) and approximately 40% water. When applied across the skin, as in case of iontophoretic treatment, an electric potential may change the molecular arrangement of these skin components. This alteration could yield some change in the skin

permeability. The 'flip-flop gating mechanism" could be an operating model for the voltage dependent pore formation in the stratum corneum which is rich in keratin, an alpha-helical polypeptide. The flip-flop of polypeptide helices may occur to form a parallel arrangement. Pores are thus opened up as a result of the repulsion between neighbouring dipole moments. The phenomenon should lead to an enhancement in skin permeability for peptide and protein molecules, and other charged molecules.

The isoelectric point of skin is between 3 and 4, which is another way of saying that pores have a positive charge below pH 3 and a negative charge above pH 4. Because of this original negative charge in the superficial skin layers, it is relatively 'easy" to introduce basic drugs through skin. Electro osmosis, the transport of liquid water as a whole, can interfere with the mechanism of iontophoresis. This leads to migration of undissociated molecules in solution. Because the skin has a negative charge, iontophoresis will effect movement of water into the body from the positive pole iontophoretically towards the outer surface of the skin at the negative pole and leads to swelling at the negative pole after intense iontophoresis. This process helpful in case of cation transfer from the positive pole, as it acts in the same direction, facilitating absorption of the cationic drugs. Electro osmosis is highest in solution with a low conductivity.

Theoretically that the skin permeating rate of an ion may not return to that characteristic of the passive diffusion immediately after removal of the electric field. This prediction is made for the following reasons. First one immediately after the electric field is removed; the concentration gradient at the dermis/receptor interface could be substantially greater than resulting from passive diffusion. The concentration gradient will gradually change with time until it becomes equal to that characteristic of passive diffusion. However, the length of time needed depend on the concentration, diffusivity and binding affinity of the permeant ion in the skin. Second one the application of an electric field may change the chemical potential of the molecules in the skin and provide sufficient energy for them to make conformational changes, which may facilitate the entry of ions. Such conformational changes could occur in structural proteins or lipids in the skin and they may or may not be immediately reversible.

Third one the application of an electric field increases the movement of water into the skin. This increase in the rate of hydration of the skin may increase the permeation rate or decrease it depending upon the major pathways taken by the ions in traversing the skin.[6]

PRINCIPLES IN IONTOPHORETIC DRUG DELIVERY SYSTEM:

Transdermal iontophoresis should be called electrically assisted transdermal delivery system. In that, three major enhancing mechanisms for drug flux through the skin membrane.

Iontophoresis:

Iontophoresis also known as Electro repulsion or Electromigtation or The Nernst Planck effect. In that, electro repulsion effect gives the largest enhancement to the flux of small lipophilic cations.[7]

The Elecromigration is characterized by the movement of charged particles in an applied electro field. In general, this is the principal mechanism by which the charged molecules are transported. The following Equation describes the dependency of the transdermal flux of each ion, on the current applied.

$$Ji = (ti/Fzi)\, I$$

ti is the transport number of species I
F is the Faraday's constant
Zi is the valence of I
I is the current intensity.

This Equation show, that current adjustment allows for direct control over the drug penetration through the skin. The transport number 'ti' is defined as the fraction of the total passing current, carried by a specific ion. It is the key parameter describing the efficiency of drug delivery by means of iontophoresis. 'ti' is dependent on the charge-carrying properties of the given ion, and the presence and properties of the co- and counter-ions involved in the iontophoretic process. The conservation of charge implies that the sum of the

electrical currents carried by each of the ions must be equal to the total current applied. In other words, the sum of all the transport numbers must be equal to 1. This means that all the ions present in the system compete amongst themselves for charge carrying.

Electro osmotic flow: [8]

Electro osmotic flow is a flux or bulk fluid induced by an applied voltage difference across a charged membrane its direction always same as the flow of counter ions. This phenomenon occurs because the skin is charged at physiological pH. When a voltage is applied across a charged membrane, a bulk solvent flow occurs. The direction of this volume flow is the same as the movement of the ions of the charge opposite to the membrane. The isoelectric point (iP) of the skin is around 4.3. So the skin is negatively charged at the physiological pH. Thus electro osmotic flow occurs from the anode to cathode direction. This impairs the transport of anions and assists that of cations.

The electro osmotic flow carries any substance dissolved in the solvent, and for that reason allows for the transdermal delivery of neutral and polar molecules. The main factors controlling the electro osmotic flow are: the pH that controls the charge density on the skin and the ionic strength, which is responsible for screening of the skin's charge. The elctroosmotic flow of compound I, can be assessed by thefollowing Equation

$$J_i^{EO} = V.C_i$$

V is the volume flow
Ci is the concentration.

Diffusion:

Most of the drugs transported across the skin membrane by the diffusion principles. More over 45% of all drugs follow this diffusion pathway. The transport stream follows the following equation[9]

$$Q = DAK (C_o - C_i)/h$$

Q = transport stream
D = diffusion constant
A = skin surface membrane
K = partition coefficient
(Co-ci) = concentration gradient between the skin membrane
h = skin membrane thickness

Under the optimal sink conditions, the drug diffusion follows the Fick's first law of diffusion. In that, the amount of drug diffusing the following manner

$$dq = -D.A\ dcdt/dx$$

dq = amount of drug molecule
D = diffusion constant
A = skin surface area
dc = change of drug concentrations
dt = diffusing time
dx = travelling distance

From the equation the flux of diffusion constant (D) decreases with increasing molecular weight.[10]

History of Transdermal Iontophoretic Drug Delivery System:

The first trial for the use of electric current in the drug delivery was carried from the mid-18th century onwards. Electric potential to enhance the penetration of charged drug molecules into the tissue was identified by the scientist notably Banga in the year of 1747. Serious research progress was made 19th century by the various scientists like Benjamin Ward Richardson (1828-1896), Hermann Munk (1839-1912), William James Morton (1846-1920), Stephen Leduc (1853-1939) and Fritz Frankenhauser (born 1868) etc., In that time period the administration of metal ions and alkaloids were tried. Until the starting period of 20th century, current medicated drug delivery was called as"cataphoresis". After that the scientist notably Frankenhauser is introduced the new technical term "iontophoresis" before the year of 1908. Now currently researchers talk about the term "electrically assisted transdermal drug delivery system".

Twenty three years ago, united states introduced the first transdermal drug delivery system making a historic breakthrough, holding the promise that the new compounds and drugs could be delivered in a safely manner, convenient way through the skin membrane and also, during the last two decades, the commercial success of transdermal delivery has been developed.[4]

Currently, iontophoresis drug delivery system across skin or mucosal membrane is a non-invasive (needleless) technique. In that the rate of drug delivery is primarily estimated by the magnitude of the applied electrical current, making patterned and on-demand delivery achievable. Commercially available drug delivery devices are bench-top systems with the discrete patches connected into a power supply by electrical cables. However, the recent innovations in the electronic circuit and the power supply battery technology, iontophoretic drug delivery can possible with small, integrated patch-like system.

Advantages of Iontophoretic Drug Delivery System:

1. It is a non-invasive technique.
2. It eliminates the problems like drug toxicity, adverse drug reactions in the formulations.[11]
3. It may allow lower quantities of drug when compared to other drug delivery methods.
4. Transdermal drug delivery system of most of the ionized drug at therapeutic levels was precluded by their slow rate of diffusion under a concentration gradient, but iontophoresis enhanced flux of ionic drugs across skin by the use of applied current potential gradient.
5. Iontophoresis delivery system prevents variation in the absorption of transdermal drug delivery system.[12]
6. Avoid the chance of over or under dosing by continuous delivery of drug programmed at the needed therapeutic rate.
7. It provide simplified therapeutic regimen.[13]
8. Patient compliance.
9. It provides a rapid termination of the drug action if needed, simply by switch of drug input from the iontophoretic delivery system.
10. It permits predictable and extended duration of action.
11. Minimize the frequency of dosage.
12. Self- administration is possible in that delivery system.
13. Systemic delivery of peptide or protein based macromolecules, which are very potent, extremely short acting and also provide delivery in a circadian pattern to simulate physiological rhythm likes thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, interferon, and encephalin etc.,
14. It avoids contamination of drug reservoir for the extended period of time.
15. Iontophoretic device system consists of an electronic control module. It would allow for time varying of free-back controlled drug delivery.
16. This system minimize the inter and intra subject variation through a constant current iontophoretic system and the device adjust automatically, the magnitude of the electrical current potential across the skin.[1]

Limitations:

1. An excessive current density usually leads to pain
2. Burns are caused by change of electrolyte concentrations within the tissues.
3. The safe current density varies with correspond to change of size electrodes.
4. This change in pH may leads to the sweat duct plugging perhaps and also precipitate protein in the ducts.
5. High current density may leads to Electric shocks at the skin surface.
6. Chances of cardiac arrest due to excessive current passing through heart.
7. Ionic form of drug in sufficient concentration is necessary.
8. High molecular weight from 8000 to 12000 leads in a very uncertain rate of delivery.[1]

Advantages over Other Drug Delivery System:

When compared with injections, this iontophoretic process:

1) Avoid the pain and invasion.
2) Reduces the needle-pricking accidents.
3) Permit its drug delivery by skin contact itself.
4) Can be used outside the hospitals also.

When compared to pills:

1) Reduces the on-set time.
2) Adverse effects alleviation.
3) Through this delivery process, it is possible to deliver the drugs which dissolve and lose their potency and efficacy in the digestive organs.

When compared to patches (adhesive):

1) Minimizes the on-set time.
2) Drugs can be delivered at quantitative manner.
3) Minimizes the residual drug amount.

Factors Affecting the Iontophoretic Transdermal Drug Delivery System:

Physiochemical properties of the compound:

Molecular size of drug:

The permeability coefficient in positively charged, negatively charged and uncharged solute drug molecules across excised human skin membrane is depend on the range of molecular size. When the permeability coefficient decreases with the increase of molecular size.

Charge:

Charge on a molecule is an important physico-chemical property governing iontophoretic transport, since the sign of the charge determines the mechanism by which iontophoresis will proceed e.g., elecrorepulsion or electro osmosis. However the transport of cations has been shown to be better than anions for amino acids and peptides. Although is not so simple because an increase in charge will need pH to be decreased, which in turn shall directly decrease the electro osmosis and electrotransport process.

Drug concentration:

The type of the drug molecule used, the steady state flux (drug ion movement) has been reported to increase with increasing concentration of the solute drug molecule in the donor chamber.i.e. In the drug delivery electrode. A limiting range to be considered is the strength of the current applied. At the high level drug ion concentrations, the movement may become independent of concentration, due to reason of the saturation of the skin boundary layer relative to the donor bulk solution

Drug salt form:

It is identified that the different salt forms have different specific conductivities and that conductivity experiments *in vitro* will provide the information related to the general suitability of a drug for the iontophoretic drug delivery system. The estimation of drug amount in the ionized state depends on the salt form along with the consideration of pH of the drug solution.[14]

Buffer system:

Buffer system is also one of the parameter involving the permeation of drug molecules by the iontoporetic drug delivery system. It is important to optimize the concentration of buffer system and should be sufficiently high to maintain the good buffer system but should not reach a too much an extent. Because the current is mostly carried by the buffer system instead of the drug, which may leads to low efficiency of iontophoretic drug permeation, while drug delivery time.

Influence of pH:

The optimum pH is an important factor in the iontophoretic drug delivery system. The optimum is a drug molecule that exists predominantly in an ionized form. If the pH decreases, the concentration of hydrogen ions increases, and it causes the vascular reaction (vasodilatation) is initiated due to C-fiber activation.[15]

It is important to maintain the pH as nearer as possible to 7, at least when research work with vasodilators. At the below level of pH 5.5, there is

an increasing risk factor for vasodilatation due to the high concentration of hydrogen ions rather than the drug molecule used in the formulation.

Ionic competition:

The sodium electrode containing solution, there is an equal quantity of negative (cl^-) and positive (Na^+) ions possible. In this migration of a sodium ion requires that an ion of the opposite charge molecule is in close vicinity. The latter ion molecule of opposite charge is called to as a counter-ion and an ion of equal charge but of a different type is called to as a co-ion.

In the iontophoresis drug delivery system, there is an important to know the adjustment of pH is performed by the addition of buffering agents. The usage of buffering agents adds co-ions which are usually smaller and more movement than the drug ion to be delivered. This leads in a reduction of the number of drug ion molecules to be delivered through the skin barrier by the applied current. For example, when a positively charged drug molecules is diluted with a saline solution, the sodium ion molecule will compete with the amount of drug molecule ions to be delivered. Ideally the addition of a buffer system should be avoided in the iontophoresis process, but if it is not possible, alternative buffers consisting of ions with low movement of mobility or conductivity are preferred for the iontophoresis.[15]

Type of matrix containing the drug: gel vs. solution:

The migration of drug molecule under the application of electrical current will be different when the matrices are different. This can be depending on viscosity, material electrical charge and porosity.[14]

Stability of the drug delivery in the iontophoretic system:

The drug selection in the iontophoretic must be stable in the solution form of formulation in the environmental condition up to the time of iotophoresis and also the iontophoretic drug delivery process. The drug oxidation or reduction may not only decrease the total drug content in the formulation. It will affect the trans membrane rate by the degradation compounds, if they possess the similar charge as the drug ion, it will competent drug ion and reduce the overall trans membrane drug delivery rate.

Current strength:

The penetrations of charged drug molecules are theoretically proportional to the intensity of current applied and also the duration of treatment. The relationship between the drug delivery rate (D) and current (I) follows

$$D = It\ M/Zf$$

t = fraction of current carried by the drug ion molecule
M = molecular weight of the drug ion molecule
Z = molecular charge per drug ion molecule
F = Faraday's constant

From the equation, the linear relationship observed the flux of drug molecule with the applied current. The electrode area used $1cm^2$ means the current is limited up to 1mA. Because above 1mA current leads to the patient discomfort and the skin irritations occurs with increasing current, the risk management of non-specific vascular reactions possible. The reason for these vascular reactions is due to the current density being high enough with a small area to stimulate the sensory nerve endings and it causing the reactions like release of substance P from C-fibre terminals.[15]

TABLE 1: EFFECT OF CURRENT ON THE BODY[18]

S.No	AC 60 Hz (mA)	DC (mA)	Effects
1	0-1	0-4	Perception
2	1-4	4-15	Surprise
3	4-21	15-80	Reflex action
4	21-40	80-160	Muscular inhibition
5	40-100	160-300	Respiratory failure
6	Over 100	Over 300	Usually fatal

Current –continuous vs. pulsed mode:

Introduction of a long period continuous current can modify the iontophoretic drug delivery process. Continuous DC current leads to skin polarization, which can minimize the efficiency of iontophoretic delivery in proportion to the length of the current application. This polarization problem can be overcome by using pulsed DC, a direct current that is delivered at periodic manner. The peptides and proteins through iontophoretic transport enhanced

by using pulsed DC when compared to conventional DC .[15]

Electrodes:
The electrodes used for iontophoretic process are to be harmless to the body and there are sufficiently flexible to apply into the body surface. Aluminium foil, platinum and silver/silver chloride electrodes are mainly used in the iontophoretic process. Among all, silver/silver chloride electrode is better choice due to its minimum electrolysis of water during the drug delivery process.

Temperature:
The penetration of drug molecule via skin is changed by dual effect of both temperature and humidity. The drug delivery process follows the Arrhenius equation and increases the drug molecule permeation with temperature.

Voltage:
The voltage applied in the iontophoretic process follows Nernst-Plank equation. In that, the flux of the ionic drug molecule due to the applied electric field is directly related to the applied voltage and charge of the drug ion molecule.

Wave form:
The waveform is also showed alter the iontophoretic drug delivery system. For example the drug delivery of insulin was highest at sinusoidal waveform when compare to square and triangular waveform.

Efficiency of drug delivery:
The efficiency of iontophoretic drug delivery can be referred as the fraction of all ions which cross over the skin of drug ion molecules which crossover the skin membrane for each mole of electron flowing through the external circuit. The efficiency of drug delivery estimated from the slope of the plot of drug delivery rate vs. applied current (I)

$$R = Ro + Fi.I$$

Ro = Positive drug delivery using iontophoresis
Fi = iontophoretic constant

Iontophoretic constant is referred as the amount of drug (on the basis of weight) delivered per unit time per unit current.

Synergistic effect of drug delivery:
The enhancement of drug molecules through the skin membrane is higher with a combination of chemical enhancers and iontophoresis, when compared to single technique is used.

Polarity:
The drug compounds having hydrophilic character is ideal for the optimum flux example nalbupline and its ester showed enhanced flux when compared to liphophilicity of drug molecule.[16]

Resistance of skin site:
The resistance of the skin in the iontophoretic process was much lower on the sweat pores, especially when they discharge in sweat.[15]

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 the iontophoresis.

Patient anatomical factors:
Patient anatomical factors also modify the drug penetration rate. This will be variable from patient to patient include thickness of skin, site of application, presence of subcutaneous adipose tissue, and size of other structures including skeletal muscle.[14]

Species variation:
While the penetration of drug, the wide variations is there in physical characteristics such as appendages per unit area, thickness and structural changes between human and laboratory animals. The average penetration of drugs in order to rabbit>rat>guinea pig>human. Permeability of human skin is very much less than other rodents but the iontophoresis of drug is 7-fold grater in human skin contain the greater negative charge or greater area fraction of negative pores.[15]

Applications of Iontophoresis Treatment:
Clinical application: In clinical therapy, iontophoresis delivery system are used particularly for the treatment of inflammatory conditions in area of skin, muscles, tendons and joints like temporomandibular joint dysfunctions. Currently,

iontophoresis has been used widely in combination with laser Doppler technology as a diagnostic purpose in disease compromising the vascular bed.

However until now the combined effect of LDPM (Laser Doppler Perfusion Monitoring) with iontophoresis has been used mostly in a diagnostic device for diseases affecting macro-and microcirculation and the controlling regulatory nerves.

Biomedical application:
Iontophoresis has wide applications in various areas such as Dermatology, Ophthalmology, and ENT, Allergic conditions even in the case of Cardiac and Neurological conditions.

Dermatology:

1. In hyperhidrosis, especially palmar and plantar-probably by obstructing the sweat ducts. No side effects when compared to anti-cholinergic.
2. In the diagnosis of cystic fibrosis to increase sweating by pilocarpine and confirm the diagnosis by the concentration of sodium and chloride in the sweat
3. In scleroderma, for iontophoretic delivery of hyaluronidase.
4. Copper-iontophoresis for fungal infection and male contraception
5. Zinc iontophoresis for ulcers
6. Iodine for reduction of scar tissues, iron/titanium for tattoo removal.[17]

Ophthalmology:
Iontophoresis of various drugs like atropine,scopolamine, sulfadiazine, gentamycin, fluorescein etc.

ENT:
For providing anaesthesia of the external ear canal and middle ear and in maxilla facial prosthetics surgeries.

Dentistry:
To provide dentin hypersensitivity and also used in local anaesthetic for multiple tooth extraction.

Delivery of drugs:
Antihypertensive, anti-diabetics, hormones, vasodilators, anti-rheumatoid, metoprolol, propranolol, insulin, methylcholine, bleomycin, steroids, have all introduced by iontophoresis

Cardiology:
Iontophoretic trans myocardial drug delivery system of anti-arrhythmic drugs which would avoid high systemic toxic levels is being done in animals.

Neurophysiological and neuropharmacological studies:
The investigation of micro-iontophoresis can be used to study neuro muscular junction, peripheral and central nervous system and smooth muscle preparations.

Musculo skeletal disorders:
Calcium for myopathy, Silver for c/c osteomyelitis, magnesium sulphate for bursitis, local anaesthetics and steroids into elbow, shoulder and knee joints.

CONCLUSIONS: This transdermal iontophoretic technique enhances the movement of drug molecules across the membrane under the influence of an externally applied electric current and hence it is one of the, most promising physical method to enhancing the skin penetration of ionic drug molecules & this article provided the complete strategy about the iontophoretic transdermal drug delivery system with respect to designing the delivery device, drug delivery mechanisms, basic iontophoretic principles, factors influencing the delivery system, various clinical & dermatological applications of transdermal iontophoretic drug delivery systems.

ACKNOWLEDGEMENT: Any attempt at any level cannot be satisfactorily completed without the support and guidance of learned people and an encouraging environment. It's a pleasure that I have a chance to express my gratitude to everyone who helped me through the course of my attempt. I wish to express my heartfelt gratitude and indebtedness to my organisation Himalaya Drug Company & My Institution Periyar College of Pharmaceitical Sciences for the support during the course of my work.

REFERENCES:

1. Swarnlata Saraf, Deependra Singh: Iontphoresis Review.Pharmainfo.net.2006; 4(1)
2. Shinde A.J, Sinde A.L, Paithane. M.B, More.H.N: Design and Evaluation of Gliclazide Transdermal Patch containing Film Former. International journal of pharmacy and Technology 2010; 3(3): 792-806
3. Chien YW: Novel drug delivery systems Drugs and the Pharmaceutical Sciences. Marcel Dekker, New York, Second Edition 1994; Vol.50: 797
4. Swati Rawat, Sudha Vengulekar, Rakesh.B, Jain.S, Srikanthi.G: Transdermal delivery by inotophoresis. Indian journal of pharmaceutical science 2008; Jan-Feb
5. N.kirubakaran, K. Reeta vijaya Rani, A.Anithaa, R. Senthamarai: design and development of iontophoretic drug delivery system of l-tyrosine, International Journal of Pharmaceutical science &Research2014; Vol. 5(12): 5382-5388.
6. Jain.N.k: Controlled and Novel drug Delivey. CBS Publishers & Distributors, New Delhi, First Edition 1997; 191-206
7. Lahoti Swaroop, Dalal Shardul.S, Rajendra Vivek.B, Dehahan M HG: Synergistic Approach of Iontophoresis with other Transdermal penetration enhancement techniques. Journal of pharmacy Research 2010; 3(1): 3051-3056
8. Edith mathiowitz: Encyclopedia of Controlled Drug Delivery. John Wiley & Sons Publishers, New Delhi, 2009; Vol. II: 967-973
9. Brahmankar D.M, Sunil B. Jaiswal: Bio pharmaceutics and pharmacokinetics a Treatise. Vallabh prakasham Publishers, First Edition 2002; 31
10. Tripathi K.D: Essential of Medical Pharmacology. Jaypee brother medical publishers, New Delhi, 2001
11. Majns Walia, lt Col BS Rathore, Col AK Jalswal: Treatment of Palmoplanter hyperhidrosis by iontophoresis. MJJAFI 2000; 56(1): 27-28
12. Reena Rani, Srinivas CR: Iontophoresis in dermatology. 2005; 71(4): 236-241.
13. Joseph R.Robinson, Vincent H.L. Lee: Controlled drug delivery fundamental and application. Marcel Dekkar Publishers, New York, Drugs and the Pharmaceutical sciences 1978; Vol. 29:524-549.
14. Grond.S, Hall.J, Spacek.A, Hoppenbroucuers, Richarz.U, Bonnet.F: Iontophoretic Transdermal System using Fentanyl Compared with Patient-Controlled intravenous analgesia using morphine for Post-operative Pain management. British Journal of Anesthesia 2007; 98(6): 806-815
15. Bertil Gazelins. Iontophoresis theory. Www. Perimed-instruments.com /broehures/iontophoresis.
16. Sanjula Baboota, Nitin Dixit, Vikas Bali, Alka Ahuja, Javid Ali: Iontophoresis-An Approach for Controlled Drug Delivery: A Review. Current Drug Delivery Vol. IV. 2007; 1-10
17. Mary Korula: Iontophoretic Delivery of Drugs. The Indian Anesthetists forum-on-line Journal (www.theiaforum.org) 2004
18. Monograph: L-Tyrosine. Alternative Medicine Review 2007; 12(4): 364-368
19. Tomasz Giller: Iontophoretic delivery of selected anti-parkinsonism agents in vitro. PhD thesis, University of Bath (United Kingdom) 2009; 1-51
20. Indian Pharmacopoeia (I.P) 1996; Vol.II: 144-145
21. Yi-Hung Tsai, Jia-You Fang, Tsong-Long Hwang, yaw-Bin Huang: Transdermal iontophoresis of sodium nonivamide acetate V. Combined effect of physical enhancement methods. Ijpharm, Vol .235 2001; 95-105
22. Vyas S.P, Roop.K.Khar: Controlled Drug Delivery Concepts and Advances. Vallabh prakasham, New Delhi, First Edition 2002; 3-7
23. Reynold C. Rowe, Paul T Shesnay, Paul Tweller: Hand book of pharmaceutical excipients Forth Edition 2005; 670-221
24. United States Pharmacopeia (USP-25/NF-20) First Annual Asian Edition 2002; 538
25. Sean C. Sweetman: Martindale the complete drug reference. Pharmaceutical Press Publishers, Thirty Third Edition, Great Britain 2003; 1631.1
26. Ansel. H.C, Loyd. A.V, Popovich. N.G: Pharmaceutical dosage forms and drug delivery systems. Lippincott Williams and Wilkins publication, Eight Edition 2004; 298-30
27. Maryadele J.O.Neil, Ann Smith, Patricia E.Heckelman. The Merck index. Marck and Co Publishers, USA 2001; 8716
28. Saqib Zafar, Asgar Ali, Mohammed Aqil, and Abdual Ahad: Transdermal drug delivery of Labetalol Hcl: Feasibility and effect of penetration enhancer. Journal of Pharmacy and Bio allied sciences 2010; 2(4): 321-324
29. Patel N.B, Sonpal R.N, Mohan, Selvaraj: Formulation and Evulation of iontophoretic Transdermal Delivery of Diltiazem Hcl. International Journal of Research Pharmaceutical sciences 2010; 1(3): 338-344
30. Anke Sieg, Valentine Wescotte: Diagnostic and therapeutic applications of iontophoresis. Journal of Drug Targeting 2009.
31. Inayat Bashir Pathan, Mallikarjuna Stty.C: Chemical penetration enhancers for Transdermal Drug Delivery Systems. Tropical Journal of Pharmaceutical Research 2009; 8(2): 173-179
32. Heather A.E.Bensou: Tramsdermal Drug Delivery: Penetration Enhancement Techniques Current Drug Delivery Vol. II 2010; 23-33
33. Rachna Prasad, Veenakoul, Such Anand, Rope K Khar: Transdermal Iontophoretic Delivery of Methotrexate. Trends Biomater.Artif. Organs 2005; 18(2) www.sbaoi.org.
34. Ardshir Arzi, Mohsen Rezaei: The effect of Oral Administration of L-Tyrosine, Folic acid and Pyridoxine on Perrphenazine Induced Catatonia in Rat. Indian Journal of Pharmaceutical Research 2003; 167-171
35. Rajkumar Conjeevaram, Ayyappa Chaturvedula, Garu V.Betageri, Gangadhar Sunkaran, Ajay K. Banga: Iontophoretic *in vivo* Transdermal Delivery of β Blockers in Hairless Rats and Reduced skin irritation by Liposomal Formulation Pharmaceutical Research 2003; 20(9): 1496-1501
36. Sang-Chul Shin, Jin Kim, Mi-Kyong yoon, In-Joon Oh Jun-Shik Choi: Transdermal delivery of triprolidine using TPX Polymer membrane. International Journal of Pharmaceutics, Vol.235, 2002; 141-147
37. David W. Osborne, Jill J. Henke: Skin penetration enhancers cited in the Technical Literature. Pharmaceutical Technology 1997.
38. Growdon. J.H, Melamed .E, Hefti.F, Wurtman R.J: Effect of oral L-Tyrosine administration on CSF tyrosine and homovanillic acid levels in patients with Parkinson's disease. Life Science1982; 30(10): 827-832
39. Bruce S. Glaeser, Eldad Melamed, John H. Growdon, Richard J. Wurtman: Elevation of plasma Tyrosine after A Single Oral of L-Tyrosine. Life sciences, Vol. 25, 1979; 265-271.

How to cite this article:
Kirubakaran N, Chandrika.M and Rani KRV: Iontophoresis: Controlled Transdermal Drug Delivery System. Int J Pharm Sci Res 2015; 6(8): 3174-84.doi: 10.13040/IJPSR.0975-8232.6(8).3174-85.