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Iontophoresis-Models and Applications: A Review

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Abstract: Iontophoresis is the technique used for the delivery of drug. It is a non-invasive technique. The review focuses on approaches, models and factors affecting iontophoresis. Different Models have been studied for transdermal and ophthalmic delivery of drug. The technique is used to enhance the delivery of drug via transdermal and topical route. It uses the low voltage electric current for the delivery of drugs. Iontophoretic devices have gained importance worldwide. These are used to enhance the bioavailability and better absorption and fast delivery of drugs. In this review various uses and applications of the iontophoresis technique are discussed.

Key words: Iontophoresis · Non-Invasive · *In Vitro* and *In Vivo* Models · Iontophoretic Devices

INTRODUCTION

Iontophoresis is a non-invasive technique, which uses electric current to deliver the charged or neutral molecule through synthetic or biological membrane. It helps to increase the penetration of ionized drug. The technique utilizes a same small amount of current for the delivery of drug. The technique for ocular Iontophoresis was first developed by German Scientist Wirtz in 1908, who conducted experiment by passing the electric current through the electrolyte saturated cotton sponges for the treatment of various eyes diseases [1].

The molecules that are delivered by the help of Iontophoresis techniques should to posses some charge on them either cationic or anionic. Due to high charge density and high solubility, the salt form of the drug is used. Ionized drug concentration in the solution should range from 0.01-5% [2]. This technique is the novel technique for the delivery of drug. Other recent techniques evolved for the delivery of drugs used in conjunction with Iontophoresis are Electroporation, Sonophoresis, ion exchange materials and Microneedles [3]. The major application of Iontophoresis technique is seen through the transdermal route. Other routes used are ocular, cardiac and buccal. Components needed for the delivery of the drug molecules are:

- Power source for generating controlled direct current.
- Electrode that contain and disperses the drug.
- Positively or negatively charged aqueous medication of relatively small molecule size (less than 8000 Daltons).
- Localized treatment site.

Principle of Iontophoresis: It is based on the mechanism of current flow, like charges repels each other while unlike get attracted. The positive charged ions in the solution are repelled from positive charged electrode which is positioned on the tissue on which the drug molecules has to be delivered, similar way for the negative ions at negative electrode. The direct current is used for the transfer of the ions from the drug electrode. The external energy is used to increase the rate of drug delivery. Neutral molecule moves by connective flow due to electro osmotic and osmotic force by the application of current. During Iontophoresis, electromigration of ion occurs which causes solvent motion and this motion helps in the movement of neutral as well as charged ions.

In Transdermal system, at a pH above 4, the skin acts as a negative charged electrode and the positive charge molecule such as Na^+ can be easily transported as it neutralizes the skin and maintains the elctroneutrality. By the loss of sodium ion the chloride ion moves in the opposite direction that is from cathode to anode and

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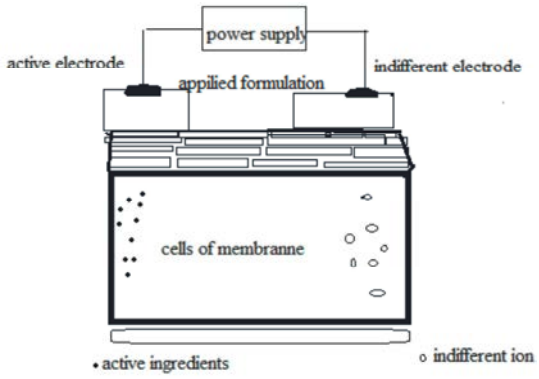

Fig. 1: Movement of ions through Iontophoresis

shows counter ion effect. Due to this process an electrochemical gradient is maintained and water flows from anode to cathode meantime if any neutral molecule is present over here will also be transferred along with it.

In ophthalmology-In the posterior segment the ocular concentration is obtained either by systemic administration or by drop administration that depends on the passive penetration of drug. The drug can be delivered by the application of current that is by the application of external electric field. Following the principle of electricity that is, like pole repel each other it means the delivery of the negative charged drug the negative electrode should be placed on the surface, the particle gets attracted towards positive electrode (which is placed away from the negative electrode).

Advantages of Iontophoresis: Advantages of Iontophoresis technique are as follows [4]:

- The technique is painless when properly applied.
- This technique is an alternative to injection and helps to deliver ionized and unionized drugs. It improves the delivery of polar molecules and high molecular weight compounds.
- The risk of infection is reduced since the treatment through this technique is non-invasive in nature.
- It is less time consuming. Treatment is completed within a minutes.
- It reduces potential for tissue trauma reducing the variability between the individuals, as the drug delivery rate is dependent on applied current.

Factors Affecting Iontophoresis: There are various factors that affect the technique of Iontophoresis. The major factors are listed as follows [5-7].

- Ionization and electrolysis.
- Effect of pH.
- Electro osmosis.
- Pore transport
- Penetration and distribution of ions.
- Skin injury.
- Concentration of mixture and solutes.
- Molecular size.
- Physiological factor.

Ionization and Electrolysis: Ionization and movement of ions are the main factors in the Iontophoresis technique. Ionization is the process of dissociation of compound in aqueous solution forming cations (positive) and anions (negative). As the current pass, the negative charged ion goes to the positive electrode (anode) and positive ion goes to negative electrode (cathode). Ions having the opposite polarity are not transferred into the body.

Effect of pH: pH of the skin plays a key role in the transfer of the drug as the process of Iontophoresis is the transfer of ion in the presence of applied electric field. For iontophoretic delivery, the pH should be optimum in which the compound exists in ionized form. The pH plays a significant role in the delivery of protein and peptide drug. A report has been made by Mandleco, which explains that pH changes from 7 to 10.1 when the current flow is of 2 or 4 mA for half an hour. This is the major cause of irritation and discomfort on the skin which is associated with Iontophoresis. Electrodes are been developed that will provide stable pH.

Chein *et al*., has conducted the experiment which showed the iontophoretic transfer of insulin which was greater at 3.7 pH [8].

Electro Osmosis: An electrically driven flow of ions across the membrane having a net charge can induce a coupled flow of solvent called electro osmosis [9]. The solvent is the major means for the transfer ions and the dissolved substances which passes through the skin by the applications of direct current. This process is termed as iontohydrokinesis. The pH of skin ranges from 3-4. Skin carry negative charge at physiological pH 7, this increases the migration of cations at anode. If the pH is below 3 the effect will take place at cathode. The transfer of uncharged substance like mannitol, neutral thyotropin releasing hormone, thymidine can be done by the application of the potential difference at the site of skin.

Pore Transport: The anatomy of the skin plays a key role in the drug delivery. The skin consists of various pores through which drug can penetrate like sweat glands, sebaceous gland and hair follicle. Ion transfer due to electric current is from this pore. Studies done shows that current traverses major through sweat glands.

Penetration and Distribution of IONS: The physical therapy of the technique is based on this factor. Some of the studies focus on the fact that ions penetrate and concentrate in the deep tissue, while other suggests that rather than concentrate formation, they are removed by sub cutaneous circulation and are distributed in the body. Deep penetration of ions may be the cause of anesthesia.

Skin Injury: Skin injury may be occurs by the change in the pH that occurs due to the flow of direct current. This can be decreased by the prior wash of skin prior to the use of iontophoretic device, by the use of well-saturated absorbent pads for electrode, keeping the density of current less than 1 mA/in^2 at cathode and by the use of petroleum jelly where ever there are skin lesions. Burns under cathode are deeper and slower to heal than of anode. Gas bubbles seem to occur at the periphery of the electrode which is caused due to the pressure and this reduces the electrolyte effect.

Leeming *et al*., has studied that the gas bubble harm the stratum corneum due to which the pH of the skin increases and here the current is at high density [10].

Concentration of Mixture and Solutes: An increase in the concentration of solute causes bottleneck effect in which ion tends to pass from the pores that are available at the site. If the solute mixture consist of different solute and dissolved material, the ion or the molecule having the greatest charge will be able to penetrate through the skin.

Molecular Size: Permeability coefficient of the positive, negative and uncharged compounds depend on the molecular size. Both of these terms are inversely dependent, as the molecular size increases permeability coefficient decreases. Some of the molecules like insulin, vasopressin and growth hormone are able to penetrate through the skin even if they are having higher volume. The optimum molal volume for the iontophoretic support should be 150 cm^3/mol.

Physiological Factors: Iontophoretic delivery is independent on the factor like age, race, thickness, degree of hydration, nature of the skin and site of application. This technique reduces inter and intra subject variability which was the major disadvantage of passive absorption.

Iontophoretic Devices and Approaches for Drug Delivery: There are many iontophoretic devices available in the market. They are:

For Transdermal Drug Delivery: Phoresor dose controller, Iontophor II and dupel system. Many of these devices are expensive, bulky and non-programmable [11].

Iontocare is the sterilized device. It was adjusted at 4 mA. The sterilize device roller is represented on anode [12].

For Ocular Drug Delivery-ocuphor, Visulex, Eyegate: Ocuphor is composed of polyacetal sponge and is used for transscleral Iontophoresis. The drug applicator is a silicon shell that contains a silver-silver chloride ink conductive element, a hydrogel pad for drug absorption and wire that is acting as dose controller.

Visulex is made from unique membrane, which increases drug transportation and eliminate the non drug ions hence acting as the prime carrier for the transfer of drug-ions through the sclera tissue [1].

Eyegate is in annular shape and made up of soft silicon rubber. The annular well is made up of tungsten electrode which is immersed in the solution of drug which flows through the silicon tubes. The solution is infused in one chamber and in other air bubble is aspirated that maintain negative pressure this help to maintain the contact of the device with the eye [13]. Table1 summarizes some of the Iontophoretic devices along with their applications [14].

Approaches for Iontophoresis: There are numerous approaches for the drug delivery by Iontophoresis devices. These include:

- In the first approach the drug in the solution form is filled in the eye cup with internal diameter in range 5-10 mm. The cup consists of two ports- one of which helps in the delivery of drug and other holds the metal electrode. The extension of solution immersed electrode is used for the supply of current.

Table 1: Iontophoretic devices and their applications

S.No	Iontophoretic devices	Drugs	Applications
1	Lidosite	Lidocaine	Anaesthetic
2	Iomed Phoresor II	Botulinum	Hyderhidrosis
3	E-Trans	Fentanyl HCl	Postoperative pain management
4	Phoresor	Lidocaine, Epinephrine	Local dermis anaesthesia
5	Active Tek	Fentanyl HCl	Postoperative pain management

- The second approach is the use of drug which is in the form of saturated gel.

Iontophoretic Models: For the drug delivery there are various models that are being proposed on these techniques. Some of the models are ophthalmic based and some are transdermal based.

Ophthalmic Based: Ophthalmic based models like *in vitro* and *in vivo* are summarized below.

***In Vitro* Model:** One of the examples of the *in vitro* model that was used for the ocular drug- penetration evaluation was the agarose gel. It was used as the model for transdermal Iontophoresis, later Brouneus *et al* has studied the diffusion properties of some local anesthetics from the solution of drug to the 1% agarose gel that was cast in syringes with tops cut off.

Anderson *et al.,* has evaluated penetration of Dexamethasone phosphate from hydrogel patch to cylindrical-agar column. The investigation was done on the depth of penetration the role of diffusion and depot formation in the agar was studied [15].

Kamath and Gangarosa evaluated the motility of drug at different pH values. The motility of drug was measured by the help of paper electrophoresis by determining spot migration. The changes in pH of the drug depend on the pKa of the drug and hence the optimal mobility changes [16].

Perfusion cell model is the approach for the drug penetration evaluation. This cell has two ports that are helpful for the placement of electrode on the corneal side. The donor compartment consists of drug and the receptor compartment consists of buffer solution. The current density and treatment time is the two major factors that govern the drug penetration. The effect of Iontophoresis on drug permeation is more for hydrophilic drug [17].

Hastings and li has used visulex iontophoretic system for the enhancement of the dexamethasone. The Visulex applicator and the sclera of rabbit were placed between the two halves of diffusion cell and the conjunctiva is facing the applicator. The drug used in the donor compartment was 1mg of dexamesthasone phosphate and the current applied was of 1mA direct current for 1hr, the visulex system has increase the delivery of drug by two fold [18].

***In vivo* Model:** In ocular Iontophoresis there are two approaches for the delivery of the drug. It can be either through transcorneal and transscleral Iontophoresis.

Transcorneal Iontophoresis: It delivers drug at a high concentration in the anterior part of eye that is cornea, aqueous humor, ciliary body, iris and lens and this helps to treat the diseases that happen in the anterior segment of eye like keratitis, glaucoma, dry eyes, corneal ulcers and ocular inflammations. Various studies have been proposed that showed the penetration of various antibiotics after the iontophoretic treatment in the anterior segment. Some of the antibiotics (Gentamicin, Ciprofloxacin and Tobramycin) delivery by Iontophoresis decreases the bacterial colonies in cornea as compared to the administration of eye drop [19].

Steroids like Dexamethasone had shown greater extent of corneal penetration in corneal Iontophoresis than the positive charged antibiotics. The study based on pharmacokinetics model estimated the distribution profile and elimination rate after the transcorneal administration by Iontophoresis technique of antibiotics.

Fishman *et al.,* has examined the maximum concentration of Gentamicin in cornea and aqueous humour after 30min and in vitreous humor after 16hrs of administration of drug by using Aphakic rabbits. In similar manner Grossman has reported the higher concentration of gentamicin by the use of higher current density that is 2.8 mA/cm^2 and the peak concentration of drug was determined [20,21].

Transscleral Iontophoresis: The diaphragm of lens and iris limits the entry of the drug to the posterior tissue of eye that is vitreous humor and retina. It crosses the barrier of posterior segment. The device is placed over the pars-plana area to avoid the damage to conjunctiva by the current. It is an alternative for systemic therapy and used

to cure the posterior ocular disorder. Gentamicin, Cephazolin, Ticacilin, Amikacin and Vancomycin have been successfully administered through this technique in the vitreous humor of rabbit.

Barza *et al.,* studied the efficacy of Gentamicin after the transscleral delivery for the treatment of Pseudomonas endophthalmitis. The delivery through this technique was used to decrease the bacterial colony in the vitreous humor from that of injection used alone [22].

Lam *et al* has studied the penetration of Dexamethasone to the posterior segment and the current used was of high density that was 400 mA/cm^2 [23].

Behar-cohen used a 6mm diameter of eye cup covering the cornea and sclera of rat and hastings has used hydrogel applicator that was placed on cul-de-sac. The applied current was of 0.4 mA. The results showed that the treatment using Iontophoresis stopped the sign of inflammation in the anterior and posterior segment of eye.

Transdermal Based: *In vitro* and *in vivo* models based on transdermal drug delivery are discussed below in brief [24].

***In Vitro* Model:** For the evaluation of absorption of molecule, the most preferable membrane is skin. The molecule permeation is governed by laws of diffusion. The animal model used in place of skin for the evaluation of permeation of percutaneous are primates, porcine, mouse, rat, guinea mpig and snake models. The permeation of chemical through transdermal follows three pathways. They are a) through the intercellular lipid domain in stratum corneum, b) through skin appendages, c) through keratin bundles.

Netzalaff *et al*., has studied the important factor like amount of free fatty acid and triglycerides that make a difference between the species in the case of skin barriers. The lipid composition of stratum corneum is different from that of other membrane. The main lipid class consist of free fatty acids, cholesterol and cholesteryl esters [25].

Singh *et al*., has studied the skin permeability coefficients and stratum cornea reservoir of three hydrocarbons (heptanes, hexadecane and xylene) in the ear of porcine and was compared with that of human skin and it has been seen that pig skin was more permeable to the molecules [26].

Sekkat *et al*.[27] has reported that for the evaluation of transdermal drug delivery to premature neonates the differentially tapestripped porcine skin may serve as the *in vitro* model. The permeation of caffeine, Phenobarbital and lidocaine passively and the delivery through iontophoretic technique was seen. The transepidermal water loss was measured to check the barrier function of tissue. Delivery of lidocaine that was done through Iontophoresis was controlled and was independent to that of the capability of the barrier.

There was carrier based drug delivery system on chemical skin permeation enhancers, specially designed vesicles, physical and microinvasive technique. Touitou *et al.,* has tested the transport of tetrhydrocannabinol from the carrier containing 10% w/w of oleic acid/propylene glycol/ polyethylene glycol 4000/ethanol mixture. The study showed that there was an increase in the permeation of drug up to 12.8 fold as compare to that of human skin [28].

***In vivo* Model:** The absorption through transdermal route of different radio-labelled molecules was examined on human volunteers and animals. The concentration of the molecule applied on the forearm of the subjects remained same. Bartek *et al.,* has done the comparative *in vivo* study of percutaneous absorption of haloprogin, acetylcystein, cortisone, caffeine and testosterone on human and various animal species. The conclusion drawn from the study was that porcine model was comparable with that of human model than that of rats and rabbits model [29].

Wester *et al.,* has used inductively coupled plasma-mass spectrometry after their application on the skin for quantitation of biological samples of boric acid, borax and disodium octaborate tetrahydrate. The use of finite and infinite dose was compared with the methodology of drug permeation across the skin and to that of absorption data. The result obtained from that of finite dose model was near to that of *in vivo* absorption data whereas the difference of 10-fold was seen in case of infinite dose model.

For the evaluation of ethosomal antibiotics system for the cure of deep skin infection the mouse model was taken. The comparison of the applied erythromycin on the skin was done with the parentral and topically administered drug. The systemic administered erythromycin was effective. The obtained result from animal infection model was correlated with that of the data obtained from the *in vitro* fluorescent probes. A clinical trial was done on anti-infective agent that was acyclovir ethosomal and comparison was done with that of commercial product. The improvement of all evaluated clinical parameter in both parallel and cross-over arm in case of ethosomal acyclovir. The data obtained revealed the proper delivery of drug to the specific organ as demonstrated in the animal model [30].

Applications of Iontophoresis: Iontophoresis has gained its applications in different fields that is helpful for the delivery of variety of drugs. The various applications of Iontophoresis are as follows:

Hyperhidrosis: It is a common disorders, this technique is used to cure plantar and palmar hyperhidrosis. For the treatment to cure this disorder the current is passed at the strength just below the threshold and the infected region is kept in the tap water for approx half n hours. It is safe and effective process.

Diagnosis of Cystic Fibrosis: The device used to cure the cystic fibrosis is Iontophoresis of pilocarpine. This technique is commonly used in paediatrics.

Anaesthesia: The use of anaesthesia is used in superficial wound excisions, eyelid surgery, local skin biopsies. The major disadvantage of anaesthesia is pain, distortion of tissue, potential systemic absorption. The disadvantage of anaesthesia was overcome by the use of Iontophoresis technology.

Facilitation of Underlying Deep Tissue Penetration of Compounds: Iontophoresis is the most advance technique for the treatment of osteroarthritis, soft tissue rheumatism, tendonitis and deep rooted local inflammatory conditions.

In Physical Therapy: In physical therapy corticosteroids are the prime drug. They are so used because they have profound anti-inflammatory effect, less effective and can be administered in both oral and topical. Various corticosteroids are available in the form of water soluble salts, possessing negative charge and hence move towards the respective electrode in the presence of electric current. Dexmethasone with Lidocaine is used to treat the musculoskeletal disorder, where the drug has kept at positive electrode as it is a negative charge ion it is transferred to the skin [1].

CONCLUSION

As the technique of iontophoresis is invasive the application of this technique is seen in various fields like ocular, cardial, transdermal etc to cure the disease. Hence the technique has gained its importance and is widely used these days. Various models have been proposed in relation to transdermal and ocular field. Different devices have been manufactured that are helpful in the safe and effective delivery of the medicament.

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