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IONTOPHORESIS: AN APPROACH TO DRUG DELIVERY ENHANCEMENT

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ABSTRACT: The skin has been used as a medium for systemic delivery of therapeutic agents. The resistance provided by the stratum corneum is the major barrier in delivering of the agents through skin. Due to this the number of drug molecules used under this category is limited. Iontophoresis is an efficient technique for physically enhancing conveyance of molecules across skin for local and systemic effects. The main feature offered by iontophoresis is the control offered by it in dose modulation by adjustment of current applied to undergo the process. It is suitable as an alternative for parenteral route as it is pain free and cost effective technique. The flux associated with iontophoretic treatment is described along with its applications in the article. The future aspects of iontophoretic treatment and the medications currently available are included in this article. Iontophoresis as a treatment regimen has gained popularity in relatively less treatment methodology but the concept should be well popularized as it offers enhancement to transdermal drug delivery system. This system being non invasive, pain free and with minimum side effects must be made use of in most of the treatment regimen.

INTRODUCTION: When a new drug is formulated various routes of administration are considered so as to provide maximum bioavailability and effective use. The most common of them all is the oral route of administration but it also has various drawbacks of which the major ones being hepatic first pass effect and degradation of the drug due to ranging pH value in the gastro intestinal tract. Thus, transdermal route of drug delivery system comes into picture to overcome these hurdles [1]. In transdermal route of administration, the drug entity is carried across the skin for penetration into the systemic circulation from where it could easily be transported to the site of action.

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The advantage of this route is that it can act locally as well as can deliver the drug to the desired location of action. Transdermal delivery system easily overcomes the drawbacks of oral route as it prevents hepatic first pass effect and also does not fasten the drug degradation process [2]. These are formulations which are pain free to administer and thus have high patient compliance and at the same time are cost effective [3].

Very vital areas of this drug delivery system are still to be discovered but nevertheless since 1000 of years there have been formulations under this segment for both local and systemic action with minimum dosage and minimum side effects [4]. Although the topical route is still restricted to narrow range of drugs, researches to include more drug is going on in this field [5 - 8]. To know better about the topical drug delivery system, it becomes essential to know about the anatomy and physiology of the skin. Penetration of the drug entity in topical route occurs through the skin.

The hair follicles, nails, sweat glands and sebaceous glands are the modifications regarded as the derivatives of the skin tissue [9, 10]. The structure of this organ remains constant throughout the body but its thickness varies depending upon site and age of the person. From the view point of drug delivery through the skin which is known as transcellular drug delivery wherein the drug entity dissolves in the keratinocytes and is passed down the layers offer very high resistance to the flow of the drug entity. The intensity of this resistance varies depending upon the nature of the drug [9]. But along with this pathway other model includes the usage of the derivative structure to enhance penetration of the drug through skin. This pathway is called as the shunt pathway. It makes use of hair follicle, sebaceous gland or the sweat gland. These derivative structures are vascularized at the end of the structure and thus show great success in transferring drug molecule across skin [10]. To enhance the penetration activity of the drug entity various enhancers are used. Both physical and chemical methods are being used to develop enhancement technique [11]. Iontophoresis is one of the physical methods. Various penetration techniques are shown below [12].

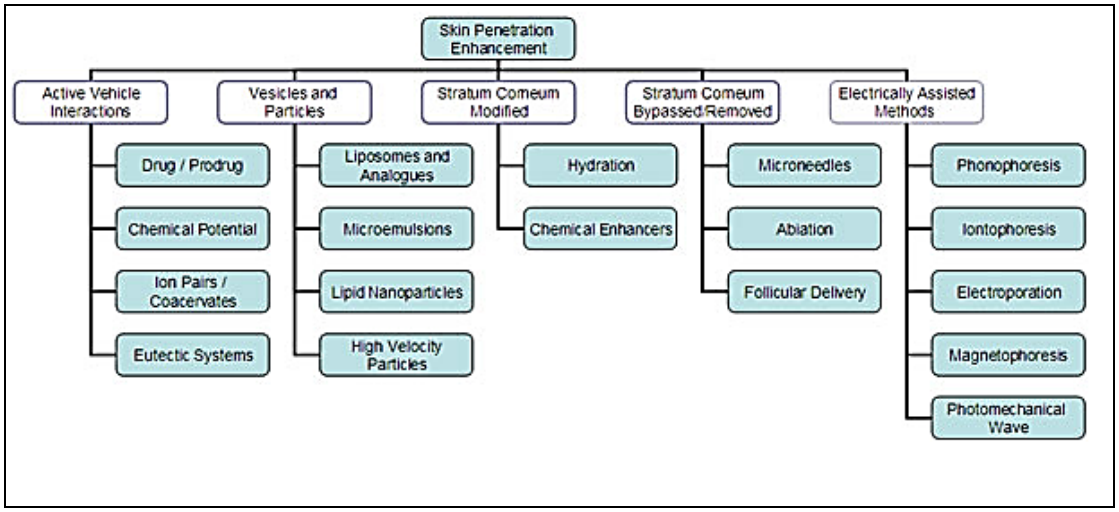

FIG. 1: PENETRATION ENHANCERS OF SKIN

Iontophoresis: Iontophoresis can be described as a process in which with the aid of electric current drugs can be penetrated through the surface tissues of the skin into the systemic circulation. Over its 200 year history this process has been applied to various conditions, among which it has found the greatest success in relieving hyperhidrosis condition [13, 22]. It is still finding various other applications [22]. Usually the electric potential applied to aid movement of drug is 0.5 mA/cm^2 or less. This technique of drug delivery is one of the most promising novel drug delivery system. This technique has qualitatively influenced the skin penetration and release rate of various drug moiety having poor absorption through layers of skin [22]. Iontophoresis is a second generation physical enhancement technique that has made a vital clinical impact due to its fast and localized delivery through skin [23] the first and third generation being the application of transdermal patches and novel innovations to expand the extent of particles respectively [24]. As this technique is driven by the application of electric potential, it gives characteristic property to it thus making it suitable for controlled dosage form [24].

Major advantages of this technique over other technique are as follows:

- Delivery of ionized and high molecular weight molecule can be made possible [25].
- Patient compliance can be improved by design that suit patient requirement such as continuous or pulsating delivery module [26].
- Formulation scientist gets better control over the amount of drug to be utilized for proper delivery as it depends upon the electric potential applied and the time duration for which it is applied [26].
- Use of this technique makes it easier to terminate the delivery process [27].

- This technique does not hinder with the skin barrier much and thus it can be restored immediately after termination of process without severe irritants.
- This technique can be used in the formulation of both drugs for systemic delivery and local delivery.
- Since the delivery of drug is dependent upon the potential applied and not on the feature of the stratum corneum there is reduction in the inter or intra variability of the drug [28].
- Control span of activity [27].
- Lessen recurrence of dose [28].
- Self-organization is conceivable [28].
- An iontophoretic framework likewise comprises of an electronic control module which would take into account time differing of feedback controlled medication conveyance [28].
- By minimizing the symptoms, bringing down the multifaceted nature of treatment and expelling the requirement for a consideration to activity, iontophoretic conveyance enhance adherence to treatment for the control of hypertension [29].
- Iontophoretic conveyance averts tainting of medications repository for amplified timeframe[30].

Thus, because of many advantages associated with this system, it has been area of growing interest in the local and systemic delivery of many drugs and shows potential development in treatment of various disease conditions.

Iontophoretic Device and Mechanism: Iontophoresis as discussed earlier is the technique involving movement of drug ion through layers of skin either to reach systemic circulation or to act topically. Thus, to accomplish this technique applies the principle of electrostatic repulsion which states "like charges have a tendency to repel whereas unlike or opposite charges show tendency to attract each other." To provide better drug penetration and maintain the concentration, the iontophoresis device acts like a complete circuit to regulate the flow of ions moving into the skin. Thus, the iontophoretic drug delivery system is composed of three components:

- **Battery:** It acts as the source for current in the circuit and some controlled electronics.
- **Electrodes:** It contains two electrodes, one anode and another cathode.
- **Reservoir:** It constitutes the drug entity to be delivered.

And lastly to complete the circuit, there is a return reservoir which constitutes generally electrolytes [34, 35]. A controlled system to monitor the process is employed to check the proper working of all the components [32,33]. A diagram showing the schematic representation of the instrument is given below.

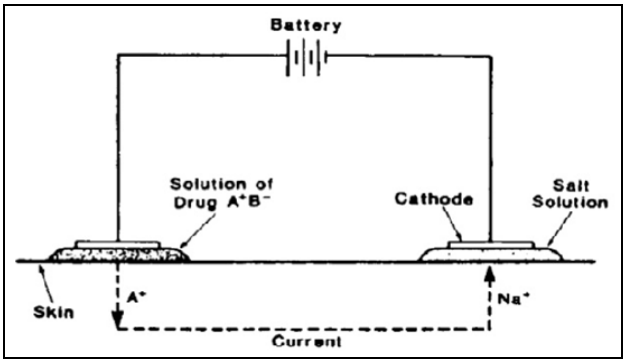

FIG. 2: SCHEMATIC REPRESENTATION OF IONTOPHORESIS DEVICE

The drug molecule or ion crosses the skin barrier due to repulsion of like charges. So now, due this principle the anionic drug can be penetrated into the skin using a negative electrode and the cationic drug can be penetrated with the help of a positive electrode. When assembling the instrument the anionic drug entity is placed between the cathode (negative electrode) and skin. Due to the repulsive force experienced by the drug it is pushed inward through the layers or stratum corneum to show its effect. It is then attracted to the anode (positive electrode) by the potential of the battery. Considering the cationic form of drug, the electrode polarities are reversed in this case [36, 37].

The movement of drug substances across the skin follows the phenomena of electro migration. During electro migration, there occurs movement of solvent and due to this movement, the ions or drug entity is pushed across the membranes along with the solvent. This process is also termed as electro osmosis [38, 63]. It thus becomes essential to know about the relation between iontophoresis flux and electro osmosis and electric mobility. For this Abramson and Gorin derived an equation.

The equation demonstrated that the generated flux during iontophoresis includes: [39]

- Flux generated due to the electrochemical potential gradient across skin.
- The effect on skin permeability due to applied electric field.
- Solvent drag due to electro osmotic water flow.

" **J(ionto)= J(electric)+J(passive)+J(convective)"**

Where:

- J(ionto) = overall flux generated; J(electric) = flux generated due to external electric field.
- J(passive) = flux generated due to passive delivery through skin.
- J(convective) = flux generated due to electro osmosis.

Due to generation of flux there are chances of disruption of the stratum corneum. To avoid this a pulsed form of the electric current is used so as to depolarize the skin and enable it to return to its original state. Pulsed waveform is employed as the stratum corneum acts like a capacitor and if it gets polarized in the process it might reduce the efficiency of iontophoresis by decreasing the magnitude of the current supplied.

Addition to this, the pulse form of current is seen to have less damaging effect on skin thus enabling the patient to tolerate high level of current frequencies. Resistance produced by the skin also needs to be considered when formulating medication in iontophoresis. Although when compared the resistance of the underneath layers of skin as well as blood is found to be lower than the uppermost layer which is the stratum corneum. But this characteristic does not confine the positioning of electrodes. But for precaution the current path should not pass across brain or heart. Normally the gap between two electrodes should be adequate around 5 to 10 cm [40-43]. Small amount of active pharmaceutical ingredient is delivered using iontophoretic devices over a given period of time. A constant voltage is maintained throughout the usage so as to vary the current depending upon the resistance provided by the skin. The resistance of the skin can be reduced by gently cleaning the skin with alcohol so as to remove the oil layer.

If there is presence of flaky skin, then it can be removed by adhesive tapes but this process should not be repeated so as to prohibit the removal of stratum corneum which might lead to loss of barrier function. This may interfere with the dosage conditions required for efficient working of equipment. Also, in these devices the current is maintained at lower than 50 micro amperes. This increases the patient compliance to the technique [44, 45]. However, the current supplied should be gradually increased at the start of the treatment and must gradually decrease towards the end of treatment.

The features required for an idea iontophoretic device are:

- ❖ It should be safe
- ❖ It should be convenient to use
- ❖ It must be reliable
- ❖ It must be economic
- ❖ It should be portable

TABLE 1: IONTOPHORETIC DEVICES

Sr. No	Name	Iontophoretic System Manufacturers	Active Pharmaceutical Ingredient	Application
1	Lidosite®	Vysteris Inc.	Lidocaine	Anaesthetic
2	IomedPhoresor® II	Iomed Inc.	Botulinum	Hyperhidrosis
3	E-Trans, ActivaTek	ActivaTek Inc.	Fentanyl HCl (Ionsys)	Postoperative pain management
4	Phoresor®	Iomed Inc.	Lidocain and epinephrine (Iontocaine)	Local dermal anesthesia
5	Ocuphor™	Iomed Inc.	-	Retinal diseases
6	Dupel®	Empi Inc.	-	Home, sports medicine and clinical settings

There are basically two types of iontophoretic devices either disposable or reusable. In reusable type the drug is formulated by incorporating into a hydro gel pad. Whereas in disposable systems,

microprocessors can be used, this can be transferred to other patches for lowering cost of treatment. Various wireless devices termed as self-contained devices are also popular with use. The electrode and stimulator are assembled in the same housing and it is can be easily used on the affected area [46-49].

Device Modifications: Iontophoresis devices come in both wired and wire free designs. The modifications of the iontophoretic device offer the physician an unparallel control over the drug delivery methodology. The wireless devices offer better compliance as they are mobile and can be used for self administration as well. In recent years iontophoretic patches are proven to do well in case of self medication therapy as they are pre-formulated and well designed to deliver correct treatment even in absence of a physician.

One of the negative parts of iontophoretic drug delivery was drying of the electrode and the base pad amidst the treatment time, that lead to excess drying of the skin, alteration of skin pH and ultimately to patient skin burns. The problem of electrode drying was rectified by inclusion of top fill ports in the iontophoretic device. The top fill ports offer quick and easy refill of the electrodes. The iontophoretic device comes in various shapes and sizes to serve the purpose of delivering medication in various parts of the body [50, 51].

Selection Criteria for Drug Candidate: The following properties must be possessed by the drug molecule to be applied into the iontophoretic delivery system:

Dose: The therapeutic dose must be low for the transdermal iontophoresis.

Low Molecular Weight: For better penetration, the molecular weight of the drug should be low, almost about 500 daltons [52].

Charge: The pH of the skin is 5.5 thus the molecular entity should possess ionizabilty at that pH.

Hydrophllicity: Should be hydrophilic in nature for efficient penetration.

Nature of Molecule: Anionic molecules are less favored than cationic molecules as the latter is accompanied in electro osmosis while that of the former is against the osmotic effect.

Stability: The drug candidate must be stable and should be stored in liquid or dry form in the patch.

Isoelectricity: The isoelectric point should be in the range of smaller than 4 or greater than 7.4 [52].

Deliverance: Drug must be delivered in the following manner - 20-50 mg drug/day of molecular weight of 300dalton and 2-5 mg drug/day of molecular weight of 1000 Da and 100 µg drug/day of molecular weight of 5000 dalton [52].

TABLE 2: DRUGS USED IN IONTOPHORESIS

Drug Solution	% Conc.	Use or Indication	Polarity
Acetic Acid	2-10%	Calcium deposits, calcified tendonitis	N
Bupivacaine HCl	0.5-1.0%	Anesthetic-Nerve Block	N
Baclofen	0.5-2%	Muscle spasm	P
Calcium chloride	2-3%	Myopathy, myopasm, immovable joints	P
Copper sulphate	2%	Astringent, fungal infection	P
Dexamethasone Sodium phosphate	0.2-1%	Tendonitis, bursitis, arthritis, tenosynovitis	N
Diclofenac sodium	0.5-1%	NSAID	N
Epinephrine	1:50000	Vasodialator	N
Fentanyl citrate	Varies	Analgesic	P
Hyaluronidase	150U/ml	Enhancement of absorption,edema, lymphedema	P
Ketoprufen sodium	10-30%	NSAID	N
LidocaineHCl	2-4%	Anesthetic nerve block	P
Salicylates	2-3%	Muscle and joint pain	P
Tolazoline hydrochloride	2%	Ulcers	P
Calcium chloride	2-5%	Muscle spasm	P

Formulation and Dosing in Iontophoresis: Iontophoresis being a physical enhancement technique for transdermal drug delivery system, a very high probability states that there is a difference in amount of dose loaded in device and the actual amount penetrating the skin layers. The amount of dose loaded on the device depends upon the technology of the device whereas the amount that crosses the skin barrier depends upon its formulation. Also due to relatively short time of delivery, formulations with long term exposure issues like low or high pH can be easily employed. These formulations offer both systemic and local effect depending upon the application. During formulation, a charged drug should be selected. One of the key components of the formulation is the agent that increases residence time that creates a depot effect. Usually aqueous or gel formulations are suited for iontophoretic treatment [53, 54].

Dose in iontophoresis is measured in milliampere-min as it is proportional to the current and the duration of the treatment. Total dosage delivered is usually calculated by the formula:

(Current × Treatment time)

Typical iontophoresis drug dose is 40 mA-min. The solutions which are placed on electrode are about 1.5ml in volume and are around 2-5% in concentration. The dosage is usually low since iontophoresis acts like a targeted delivery system. The administration can be continuous or with time intervals and can be controlled by the circuit setup. Maintain the drug dose becomes easy as the current controls the amount of drug delivered and thus it can be either for longer duration or short one. To calculate the amount of dose the following equation can be considered.

Dose (Mass) = Dose (coulombs) × Molecular Weight / (9.632 x 10000) [55].

Drug Delivery Pathway in Iontophoresis: Drug delivery indicated the amount of drug present at the site of action at the given time. The penetration of drug will not always be same for everyone as all humans are not the same. The skin characteristics are different as well as the location chosen for the use of iontophoretic devices also influence the delivery of the drug. The passive diffusion study in *in vivo* conditions for the drug methyl salicylate on skin of human provides information about the following rank: Abdomen> Forearm> Instep> Heel> Planter [56]. The drug undergoing iontophoresis must overcome the resistance of the skin and should penetrate through the layers. For this the drug in iontophoresis follows any of the percutaneous routes as discussed below.

Majorly three pathways exist in absorption of drug through percutaneous route. A combination of these pathways leads to the desired drug delivery of the medication [57]. These pathways are:

Intercellular - (paracellular) it is the pathway along the lamellar lipids in the corneocytes.

Intracellular - (transcellular) It is the pathway through the cells in the stratum corneum.

Shunt pathway - (appendageal) it is the pathway through hair follicles, sweat ducts and secretary glands present beneath the epidermis layer of the skin.

When considering the process of iontophoresis, wherein ions are transported across the skin to enter systemic circulation, the route which provides the least electrical resistance to the ions is preferred. In the stratum corneum the least electric resistance is applied by the shunt pathway. The major transport of ions takes place through sweat gland than hair follicles and sweat glands together.

When talking about drug delivery pathway the physicochemical properties of drug also play a very important role. These properties have an effect on follicular and non-follicular route of penetration like hydrophilic molecular ions tend to opt for hair follicular penetration whereas lipoidal molecular ion prefer to be distributed through intercellular region of the stratum corneum and epidermal keratinocytes [59]. Along with these pre-existing pathways, recently a non-appendageal pore pathway was also suggested which suggests current flow through “artificial shunts” which results due to transient damage of the organized structure of the stratum corneum [57, 58].

The flip flop movement of polypeptide helices allocates a potential dependent pore formation in the stratum corneum. Intercellular transport of ions also occurs simultaneously with follicular transport

but their contribution towards the total flux transport is likely small [58]. The human skin is supposed to be negatively charged at pH 4, thus it is believed to be facilitating the transport of cations of positively charged entity. The negative charge on skin is ascribed to the presence of large number of protein amino acid residues. During iontophoresis net flow volume is achieved by the resistant permeation of skin and this flow is in the direction of cathodic ions which supports the cathodic selectivity of skin [60].

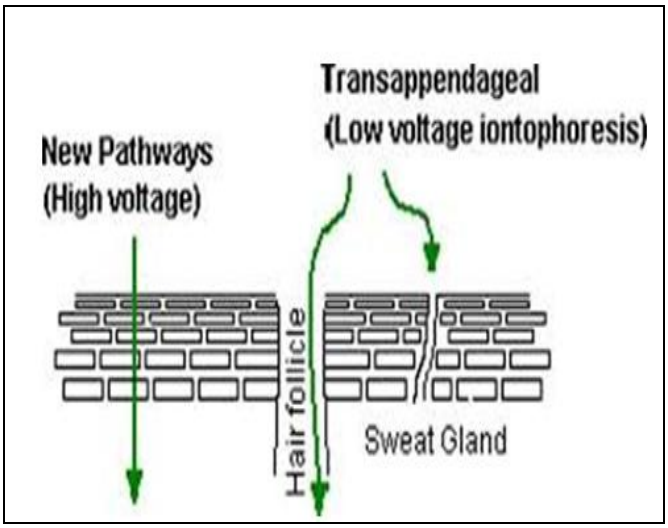

FIG. 3: IONTOPHORESIS PATHWAY OF DRUG PENETRATION

Transdermal drug delivery system has been enhanced by iontophoresis majorly by three mechanisms:

- Ion electric field interaction - this mechanism provides additional force that helps penetration of ions through skin.
- Permeability of skin is improved by the flow of electric current.
- Electro osmosis - this mechanism promotes bulk movement of solvents to carry ions or neutral species with them. It is usually in the same direction as flow of counter ions. This mechanism may assist or hinder drug transport [61]. Due to electro, osmotic flow the transport of large anion from anodic compartment is beneficial than cathodic compartment.

Factors Affecting Iontophoresis: Various factors have been observed that affect the mechanism of iontophoresis. The major factors that influence the penetration of the drug entity can be subdivided into 4 classes.

Physicochemical Properties of Compound Itself: this includes molecular size, charge and concentration of the drug molecule.

The solution: This includes the type of buffer used, pH of the solution and the presence of other compounds in the solution.

Electrical and Technical Factor: This includes different types of current, electrodes, treatment length and current density.

Biological and Physiological Factor: This includes the site, humidity, regional blood flow.

When iontophoresis is used as a diagnostic instrument these factors must be considered.

Molecular Size: Penetration of drug entities across the skin is a function of the molecular size. It is observed that as there is increase in molecular size the penetration power of the molecule decreases. Although some exceptions are available like insulin, some peptides having high molecular weight, etc.

Current: Two kinds of current are generally employed, DC and pulsed. Pulsed is more commonly used due to the advantage it offers over the DC.

Concentration: The steady state flux shows gradual increase along with the increase in the concentration of the drug entity under use placed in donor compartment. If saturation of boundary layer across donor compartment takes place, then the penetration becomes independent of concentration.

Convective Factors: The contribution of convective factor is believed to be small. But it helps to transport the uncharged substances across the skin layers due to electro osmosis.

pH: It is an important factor to be considered for iontophoretic treatments. pH should be maintained at around 7 for high efficiency of treatment. Acidic ph may lead to vascular reactions as the tendency of hydronium ions to penetrate is higher than the actual drug entity.

Ionic Competition: When adjusting the pH of the solution generally buffer is added. Due to addition of buffer the concentration of co-ions increase in

the solution. This leads to reduction in number of drug molecules to be supplied under the current as the co-ions compete with the drug molecule.

Current Strength: A linear relationship is observed between flux of amount of compound and the applied current. But still the current should be controlled below 1mA and for less than three minutes so as to avoid skin irritation [62].

Applications:

Topical Conveyance: The capacity to control the conveyance rates of medications by changes in current makes iontophoresis an appealing system for application. Yamashita *et al.*, examined the adequacy of iontophoretic conveyance of calcium for treating burns caused by hydrofluoric acid [63].

Hyperhidrosis: The success story of Iontophoresis is in the treatment of hyperhidrosis. It is a very common disorder and many people complain about being socially uncomfortable with it. The clear meaning of hyperhidrosis is excess sweating. This condition can have a localized effect or affect the whole boy. Usually the plantar and palmar regions are affected. This condition can occur due to some triggers like warm weather or excess physical activities or can also occur without a trigger. Some medical conditions like hyperthyroidism or menopause can also be the leading cause of this condition. Iontophoresis is generally applied in the treatment of plantar and palmar hyperhidrosis.

The treatment process occurs in the following way: the iontophoresis machine supplies weak electrical current to affected areas of the skin through water [64]. The electrical signal supplied is of low intensity and thus produces minimum side effect. The process is initially repeated for about thrice a week and further depending upon the desirable results the frequency of the treatment can be changed [65, 66]. The suggested mechanism used in the treatment of hyperhidrosisis: The flow of current and mineral particles through the water work in conjunction to thicken the external layer of skin, in this manner obstructing the stream of sweat. The current may upset ordinary nerve transmission, which prevents the sweat pipe from working.

Iontophoresis diminishes the pH esteem in the sweat organ, which makes it more acidic and decreases the measure of sweat created. The penetration capacity of the drug can be improved by the addition of salt or baking soda and at times some prescription medicine like Robinul or glycopyrrolate or formaldehyde for hyperhidrosis which are of anticholinergic category can be added to water [68].

Dermatology: Iontophoresis with the aid of various medicines is applied in the treatment of different types of dermatological conditions. The selection of the medicinal drug entity has seen a large drift from the most frequently used simple ions and heavy metals to wide variety of steroids, antibiotics and local anesthetics over the span of 30 years. Under this category, the various conditions discussed are as follows:

Ulcers: Ischemic leg ulcers were treated with the help of iontophoresis. Majorly the effect of histamine was studied by Abramson *et al.*, whereas corn well reported the response towards zinc oxide in iontophoresis [69].

Fungal infection: Reports on successful treatment of dermatophytosis with the use of copper sulphate and the treatment of sporotrichosis with potassium iodide in iontophoresis are present [69, 70].

Warts: Warts are described as the small, fleshy bump on skin or mucous membrane usually caused by human papillomavirus. Sodium salicylate iontophoresis is utilized in the successful treatment of plantar warts [71].

Herpes simplex: Commonly known as the herpes simplex virus that causes contagious sores. It is of two types, one called as genital herpes which is marked by genital pain and sores and the other known as oral sores which occurs at the border of lips. Idoxuridine was found to be effective in absorbing episodes of herpes as reported by Gangarosa [13]. Other advantage of iontophoretic use of the same drug lead t decrease in the healing time and discomfort of herpes as reported by Lekas [72].

Anesthesia: Anesthesia of the skin can be accomplished with the utilization of positive and negative controls, including iontophoresis of epinephrine and lidocaine independently, and topical organization of lidocaine and epinephrine[73]. Skin anesthesia is best achieved with arrangements

containing 1% and 4% lidocaine and between 1/10,000 and 1/50,000 epinephrine. Anesthetic iontophoresis might be valuable particularly for pediatric patients. Application of anesthetic iontophoresis is found in anesthesia for middle ear by otolaryngologist and anesthesia of oral mucosa by dentist [74, 75].

Scleroderma: It is described as the chronic hardening and tightening of the skin and connective tissues. Iontophoretic treatment with hyaluronidase prompted expanded skin non-abrasiveness and adaptability of tissues and diminished cold sensitivity [76]. Although cold sensitivity did not last long but the non-abrasiveness of skin lasted for about a period of three months after the end of therapy.

Ophthalmology: Due to the presence of blood retinal barriers the penetration of drug through systemic circulation in the eye is not easily achieved. There can be high chances of suffering from ocular complications in ophthalmic delivery. Iontophoresis has proved to be a successful tool in the penetration of antibiotic and anti-inflammatory drug to the eye. Depending upon the desired depth of penetration, there are two categories of iontophoresis:

- Transcorneal therapy
- Transscleral therapy

Formulations in ophthalmology are very critical issue as high concentration of drug or electric potential can lead to certain side effects which include localized burns, conjunctivital edema, mucous discharge, etc [77, 78].

Dentistry: Dentistry has utilized iontophoresis on a noteworthy degree. Dental specialists used this therapy to provide anesthesia before oral surgery. Iontophoresis is generally used in dentistry for:

- Treatment of easily affected dentin by using charged fluoride particles.
- Treatment of oral ulcers
- Exercises based on recuperation applications

For anesthesia in dentistry the revolution brought by this therapy was needle free deliverance of anesthesia which added on to patient compliance for treatment. It also reduces the risk of contamination, reduces level of intoxication and makes the process cost efficient [79].

Otorhinolaryngology: Iontophoresis is a favored strategy for acquiring anesthesia of the tympanic layer preceding basic surgical techniques including that structure. Iontophoresis of zinc has likewise been utilized for the treatment of patients with allergic rhinitis [80].

Vitamin C Treatment: Vitamin C is an essential constituent of the diet which is an immunity modulator and also prevents the formation of melanin pigment. It also imparts antioxidant property to the skin. It is generally used over sunscreens as Vitamin C can be absorbed in the cells and stay there for long duration. But the concentration of Vitamin C that can penetrate into the cell is less. This is where iontophoresis plays a major role. Vitamin C iontophoresis is useful in treating wrinkles, post inflammatory hyper pigmentation and also melisma [81, 82]. Some of the major uses of this therapy is mentioned below:

- It helps to prevent the skin from environmental and UV induced damage.
- Strengthens skin dermis by producing collagen
- Inhibits formation of malignant skin tumors.
- Reduces the appearance of skin aging
- Helps replenish the energy of the skin.
- Compatible with all skin types.

Beauty Treatment: Iontophoresis applied in the treatment of beauty regimens include ingredient such as vitamins, minerals, collagen, elastin, amino acids, hyaluronic acid and various range of plant and mineral extracts. These ingredients are used in the form of gels, serums, ampoules, etc. The general idea behind using iontophoresis in the beauty treatment is that iontophoresis increases the skin penetration capacity of these substances on a large scale thus providing high efficiency and customer satisfaction. The heat produces during the treatment results into skin reddening which is regarded as a regenerating effect which demonstrates the efficiency of the treatment. Iontophoretic treatment includes hydration, repair and regeneration of skin, provocation of poor circulation, etc. These therapies rely on the amount of drug penetrated into the skin due to iontophoresis.

To reverse the effect of the treatment which is to invert the pushing process into pulling one the fundamental applied is the reversal of electrode potential. This technique is utilized in de incrustation. De incrustation is the galvanic treatment that appears simultaneously with iontophoresis. This technique is utilized to remove the impurities that build up in the skin leading to wrinkles, pimples, acne, blackheads. These impurities thus become essential to be removed so as to replenish the skin layer with new cells. The main characteristic of this technique comprises of breaking up, decreasing and removing all the impurities which block the glandular tubes so as to increase the blood circulation and lead to re-coloring of epidermis [83, 84].

Systemic Sclerosis: Systemic sclerosis is a rare disease which is a chronic hardening and tightening f-skeletal muscle and connective tissues. This disease mainly affects the microcirculation. It can lead to ulceration of the muscle and in severe cases amputation may also be needed. For the treatment of systemic sclerosis prostacycline analogues were given intravenously to the patients who also resulted to produce potentially serious vasodilatation effects as its side effect. Thus as an alternative treatment iontophoresis system was developed with treprostinil which proved to have local therapeutic efficacy. For the treatment pulsed iontophoretic current was applied which yielded better efficacy in the case than continuous current.

Onychomycosis: Onychomycosis which is a fungal infection is a condition that affects the nail usually the toe nail and is associated with both physical and psychological morbidity. Significant causes associated are diabetes, HIV and avid sports activity. Various topical treatments prove to be ineffective due to their inability to penetrate the nail plate. Thus the application of iontophoresis is supposed to be more successful in incorporation the drug in the nail plate and passing it through the nail. The recommended drug for the treatment is terbinafine as it has shown to have highest antifungal effect in dermatophytes *in vitro*. There are currently two iontophoretic devices under clinical trials. Electro kinetic transungual system is a device under phase I clinical studies and power paper iontophoretic patch device is another device [90 - 92].

Future Applications: Transdermal delivery of drug is a field of huge scope in medical treatment. The application of this system is easy and can be easily controlled. The issues in iontophoresis treatment arise due to the electrical properties of the skin which act as a barrier to provide protection.

A new gateway for iontophoresis as a technique of drug delivery due to the complexity of skin structure is under process. Various substances present in the sector are very difficult to convey by inactive propagation. Thus, iontophoresis can enable the conveyance of these substances with ease indicating an excessive amount to look forward in the framework.

To increase the impact of iontophoresis in drug conveyance, various combinations of chemical and physical enhancers can be used along with iontophoresis for quality in treatment. Another implication would be to make the treatment cost effective for the purchaser so that the use can be popularized. Future patterns for innovation would incorporate penetration of different medications from the same patch with more extensive figuring abilities. Another area of interest under this segment would be neurology. The utilization of iontophoresis is increasing at a phenomenal rate of 12% per annum which indicates an expansion of market value by $31.5 billion until 2015 [84-88].

CONCLUSION: It should be evident from this review that iontophoresis hold a lot of promise for drug delivery. Iontophoresis can be applied in both the cases to treat local as well as systemic effects. It is helpful in targeting underlying tissues in cases of muscular skeletal disorders. It can be considered as a practical alternative of parenteral route of administration as the plasma level concentrations are significant in nature. This method of drug delivery offers high patient compliance with cost effectiveness of the treatment.

This treatment being easy to use in nature can be self-monitored. The delivery of poorly water soluble compounds can also be made possible by combining this technique with other penetration enhancer models. Iontophoresis lies close to commercialization while the research investigators intensify in the combined area of use.

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REFERENCES:

1. Rastogi V and Yadav P: Transdermal drug delivery system: An overview. Asian Journal of Pharmaceutics 2012; 6(3): 161.
2. Srinivasan V and Higuchi W: A model for iontophoresis incorporating the effect of convective solvent flow. International Journal of Pharmaceutics 1990; 60(2): 133-8.
3. Nordstrom A: What will it cost to attain the health MDGs? Bulletin of the World Health Organization 2007; 85(4): 246.
4. Kalia YN, Naik A, Garrison J and Guy RH: Iontophoretic drug delivery. Advanced Drug Delivery Reviews 2004; 56(5): 619-58.
5. Transdermal drug delivery: Developmental issues and research initiatives. Drugs and the pharmaceutical sciences series 35 edited by J. Hadgraft and R.H. Guy. European Journal of Medicinal Chemistry 1989; 24(1): 101.
6. Williams A: Transdermal Drug Delivery. International Journal of Pharmaceutics. 2003; 261(1-2): 171.
7. Prausnitz MR, Mitragotri S and Langer R: Current status and future potential of transdermal drug delivery. Nature Reviews Drug Discovery 2004; 3(2): 115-24.
8. Murdan S: Percutaneous Absorption, Drugs - Cosmetics - Mechanisms - Methodology, 3rd Edition, Edited by R.L. Bronaugh and H.I. Maibach, Marcel Dekker Inc., New York. International Journal of Pharmaceutics 2000; 210(1-2): 121.
9. Ro BI and Dawson TL: The Role of Sebaceous Gland Activity and Scalp Microfloral Metabolism in the Etiology of Seborrhea Dermatitis and Dandruff. Journal of Investigative Dermatology Symposium Proceedings 2005; 10(3): 194-7.
10. Ogan L: Dermatology. An Illustrated Colour Text, 2nd edn. By D.J.G awkrodger. Edinburgh: Churchill Livingstone. Clinical and Experimental Dermatology 1998; 23(3): 143.
11. Touitou E, Junginger H, Weiner N, Nagai T and Mezei M: Liposomes as Carriers for Topical and Transdermal Delivery. Journal of Pharmaceutical Sciences. 1994; 83(9): 1189-203.
12. Singh J and Singh S: Transdermal Iontophoresis: Effect of Penetration Enhancer and Iontophoresis on Drug Transport and Surface Characteristics of Human Epidermis. Exogenous Dermatology Current Problems in Dermatology 179-83.
13. Licht S: Therapeutic Electricity and Ultraviolet Radiation. Southern Medical Journal 1960; 53(9): 1202.
14. Anderson CR, Morris RL, Boeh SD, Panus PC and Sembrowich WL: Effects of Iontophoresis Current Magnitude and Duration on Dexamethasone Deposition and Localized Drug Retention 2003; 83: 161-170.
15. Clemessy M, Couarraze G, Bevan B and Puisieux F: Preservation of skin permeability during in vitro iontophoretic experiments. International Journal of Pharmaceutics 1994; 101(3): 219–26.
16. Sims S, Higuchi W and Srinivasan V: Skin alteration and convective solvent flow effects during iontophoresis: I. Neutral solute transport across human skin. International Journal of Pharmaceutics 1991; 69(2): 109-21.
17. Kalaria DR, Dubey S and Kalia YN: Clinical Applications of Transdermal Iontophoresis. Topical and Transdermal Drug Delivery 2012; 3: 67–83.
18. Fundamentals of Rate-Controlled Drug Delivery. Drugs and the Pharmaceutical Sciences Novel Drug Delivery Systems, Second Edition 1991; 43-137.
19. Singh P and Maibach HI: Iontophoresis: an alternative to the use of carriers in cutaneous drug delivery. Advanced Drug Delivery Reviews 1996; 18(3): 379-94.
20. Kavanagh G, Oh C and Shams K: BOTOXR delivery by iontophoresis. British Journal of Dermatology 2004; 151(5): 1093-5.
21. Alza product literature www.alza.com.
22. Srinivas C, Rai R. Iontophoresis in dermatology. Indian Journal of Dermatology, Venereology and Leprology. 2005; 71(4):236.
23. Kassan DG, Lynch AM and Stiller MJ: Physical enhancement of dermatologic drug delivery: Iontophoresis and phonophoresis. Journal of the American Academy of Dermatology 1996; 34(4): 657-66.
24. Scheindlin S: "Transdermal Drug Delivery: Past, Present, Future " Molecular Interventions 2004; 308-12.
25. Srinivasan V, Higuchi WI, Sims SM, Ghanem AH and Behl CR: "Transdermal Iontophoretic Drug Delivery: Mechanistic Analysis and Application to Polypeptide Delivery." Journal of Pharmaceutical Sciences 1989; 78(5): 370-75.
26. Phipps JB, Padmanabhan RV and Lattin GA: "Iontophoretic Delivery Model Inorganic and Drug Ions." Journal of Pharmaceutical Sciences 1989; 78(5): 365-69.
27. Herwadkar A and Banga AK: Transdermal Delivery of Peptides and Proteins. Peptide and Protein Delivery 2011; 69-86.
28. Kalia YN, Naik A, Garrison and Guy RH: Iontophoretic drug delivery. Advanced Drug Delivery Reviews 2004; 56(5): 619-58.
29. Zakzewski CA and Li JK-J: Pulsed mode constant current iontophoretic transdermal metaprolol tartrate delivery in established acute hypertensive rabbits. Journal of Controlled Release 1991; 17(2): 157-62.
30. Delgado-Charro MB: Iontophoretic drug delivery across the nail. Expert Opinion on Drug Delivery 2011; 9(1): 91-103.
31. Parry CBW: S. Licht ed., Therapeutic Electricity and Ultraviolet Radiation. Rheumatology 1960; 5(5): 182-3.
32. Wolff MS, Bronaugh RL and Maibach HI: Percutaneous absorption: Mechanisms-methodology-drug delivery. Edited by. Marcel Dekker, Inc., New York, NY. Second Edition, Revised and Expanded, American Journal of Industrial Medicine 1990; 17(5): 643.
33. M: Transdermal drug delivery: approaches and significance. Research and Reports in Transdermal Drug Delivery 2012; 1.
34. Jain NK: Controlled and Novel Drug Delivery. 1st ed. New Delhi: CBS publishers and distributors 1997.
35. Singh P and Maibach HI: Iontophoresis: an alternative to the use of carriers in cutaneous drug delivery. Advanced Drug Delivery Reviews 1996; 18(3): 379-94.

36. Patni M, Puranik P, Sonawane A and Panzade P: Transdermal iontophoretic delivery of timolol maleate. Brazilian Journal of Pharmaceutical Sciences 2012; 48(4): 819-27.
37. Gratieri T, Santer V and Kalia YN: Basic principles and current status of iontophoresis. Expert Opinion on Drug Delivery 2016; 11: 1-12.
38. Guy RH, Kalia YN, Delgado-Charro M, Merino V, López A and Marro D: Iontophoresis: electro repulsion and electro osmosis. Journal of Controlled Release 2000; 64(1-3): 129-32.
39. Gratieri T, Santer V and Kalia YN: Basic principles and current status of transcorneal and transscleral iontophoresis. Expert Opinion on Drug Delivery 2016; 11: 1-12.
40. Clemessy M, Couarraze G, Bevan B and Puisieux F: Preservation of skin permeability during in vitro iontophoretic experiments. International Journal of Pharmaceutics. 1994; 101(3): 219-26.
41. Srinivasan V and Higuchi W: A model for iontophoresis incroporating the effect of convective solvent flow. International Journal of Pharmaceutics 1990; 60(2): 133-8.
42. Guy R and Delgado-Charro MB: Iontophoresis. Transdermal Drug Delivery Systems 2002;
43. Dixit N, Bali V, Baboota S, Ahuja A and Ali J: Iontophoresis - An Approach for Controlled Drug Delivery: A Review. Current Drug Delivery 2007; 4(1): 1-10.
44. Sage BH and Riviere JE: Model systems in iontophoresis - transport efficacy. Advanced Drug Delivery Reviews 1992; 9(2-3): 265-87.
45. Dhote V: Iontophoresis: A Potential Emergence of a Transdermal Drug Delivery System. Scientia Pharmaceutica 2012; 80(1): 1-28.
46. Kavanagh G and Shams K: Delivery of Botox R by iontophoresis: reply from authors. British Journal of Dermatology 2005; 153(5): 1076.
47. Alza product literature www.alza.com.
48. Iomed product literature http:// www.iomed.com.
49. Chaturvedula A, Joshi D, Anderson C, Morris R, Sembrowich W and Banga A: In vivo iontophoretic delivery and pharmacokinetics of salmon calcitonin. International Journal of Pharmaceutics 2005.
50. Welcome to WR Medical, http://wrmed.com/home.aspx.
51. https://www.ncmedical.com/activatek, accessed on.
52. Jacobsen J: Buccal iontophoretic delivery of atenolol•HCl employing a new in vitro three-chamber permeation cell. Journal of Controlled Release 2001; 70(1-2): 83-95.
53. Green PG: Iontophoretic delivery of peptide drugs. Journal of Controlled Release. 1996; 41(1-2): 33-48.
54. Kotwal V, Bhise K and Thube R: Enhancement of iontophoretic transport of diphenhydramine hydrochloride thermosensitive gel by optimization of pH, polymer concentration, electrode design, and pulse rate. AAPS PharmSciTech 2007; 8(4): 320-5.
55. Stamatialis D, Rolevink H, Girones M, Nymeijer D and Koops G: In vitro Evaluation of a Hydroxypropyl Cellulose Gel System for Transdermal Delivery of Timolol. Current Drug Delivery 2004; 1(4): 313-9.
56. Riva CE: Laser Doppler Techniques for Ocular Blood Velocity and Flow. Ocular Blood Flow 2012; 123-46.
57. Cross SE, Anderson C and Roberts MS: Topical penetration of commercial salicylate esters and salts using human isolated skin and clinical microdialysis studies. British Journal of Clinical Pharmacology 2002; 46(1): 29-35.
58. Cullander C: What are the pathways of iontophoretic current flow through mammalian skin? Advanced Drug Delivery Reviews 1992; 9(2-3): 119-35.
59. Yoshida NH and Roberts MS: Structure-transport relationships in transdermal iontophoresis. Advanced Drug Delivery Reviews 1992; 9(2-3): 239-64.
60. Curry SH: Novel drug delivery systems, Y. W. Chien. New York, Marcel Dekker Inc., Biopharmaceutics and amp; Drug Disposition 1983; 4(4): 405.
61. Dutet J and Delgado-Charro MB: Electro osmotic transport of mannitol across human nail during constant current iontophoresis. Journal of Pharmacy and Pharmacology 2010; 62(6): 721-9.
62. Pikal MJ: The role of electro-osmotic flow in transdermal iontophoresis. Advanced Drug Delivery Reviews 2001; 46(1-3): 281-305.
63. Kanikkannan N: Iontophoresis-Based Transdermal Delivery Systems. Bio Drugs 2002; 16(5): 339-47.
64. Yamashita M, Yamashita M, Suzuki M, Hirai H and Kajigaya H: Iontophoretic delivery of calcium for experimental hydrofluoric acid burns. Critical Care Medicine. 2001; 29(8): 1575-8.
65. Zlotogorski A and Shafran A: Iontophoresis in dermatology. Journal of the American Academy of Dermatology 1987; 17(4): 690.
66. Hölzle E and Ruzicka T: Treatment of Hyperhidrosis by a Battery-Operated Iontophoretic Device. Dermatology 1986; 172(1): 41-7.
67. Sloan JB and Soltani K: Iontophoresis in dermatology. Journal of the American Academy of Dermatology 1986; 15(4): 671–84.
68. Gordon BI and Maibach HI: Eccrine Anhidrosis Due to Glutaraldehyde, Formaldehyde, and Iontophoresis**From the Division of Dermatology, Department of Medicine, University of California School of Medicine, San Francisco, California 94122. Journal of Investigative Dermatology 1969; 53(6): 436-9.
69. Guffey JS, Rutherford MJ, Ayne W and Phillips C: Skin pH Changes Associated with Iontophoresis. Journal of Orthopaedic and amp; Sports Physical Therapy 1999; 29(11): 656-60.
70. Brown SI: Treatment of Herpes Simplex Keratitis with Copper Sulfate Iontophoresis. Archives of Ophthalmology 1962; 67(4): 453.
71. Shaffer LW: Sporotrichosis. Archives of Dermatology and Syphilology. 1947; 56(2): 244.
72. Treatment of Plantar Warts. JAMA: The Journal of the American Medical Association 1963; 184(9): 173.
73. Gangarosa LP, Merchant HW, Park NH and Hill JM: Iontophoresis in dermatology application of idoxuridine for recurrent herpes labialis: Report of preliminary clinical findings. Method Find Exp Clin Pharmacol 1979; 1: 105-9
74. Comeau M, Brummett R and Vernon J: Local Anesthesia of the Ear by Iontophoresis. Archives of Otolaryngology - Head and Neck Surgery 1973; 98(2): 114-20.
75. Gangarosa LP: Iontophoresis for surface local anesthesia. The Journal of the American Dental Association 1974; 88(1): 125-8.
76. Gupta B, Singh N, Saxena K and Srivastava V: Topical amiloride solution accelerates healing of mechanical skin ulcers in albino rats. Methods and Findings in Experimental and Clinical Pharmacology 2000; 22(9): 671.
77. Popkin RJ: The Use of Hyaluronidase by Iontophoresis in the Treatment of Generalized Scleroderma. Journal of Investigative Dermatology 1951; 16(2): 97-102.

78. Vollmer DL, Szlek MA, Kolb K, Lloyd LB and Parkinson TM: In vivo Transscleral Iontophoresis of Amikacin to Rabbit Eyes. Journal of Ocular Pharmacology and Therapeutics 2002; 18(6): 549-58.
79. Grossman R and Lee DA: Transscleral and Transcorneal lontophoresis of Ketoconazole in the Rabbit Eye. Ophthalmology 1989; 96(5): 724-9.
80. Richardson A: Iontophoresis of fluoride for desensitizing dentin. Journal of Dentistry 1979; 7(1): 88.
81. Lekas MD: Iontophoresis Treatment. Otolaryngology - Head and Neck Surgery. 1979; 87(3): 292-8.
82. Vitamin C Iontophoresis Treatment | Skincare Laser ClinicViet Nam.
83. Padayatty SJ: Vitamin C Pharmacokinetics: Implications for Oral and Intravenous Use. Annals of Internal Medicine 2004; 140(7): 533.
84. https://racinne.ca/iontophoresis-in-skin-care/
85. http://www.cosmeticsandskin.com/cdc/iontophoresis.php
86. Prausnitz MR, Mitragotri S and Langer R: Current status and future potential of transdermal drug delivery. Nature Reviews Drug Discovery 2004; 3(2): 115-24.
87. Formulation: http://www.google.com/patents/US2010033 1812.
88. Mechanism of iontophoresis: http://www.electrotherapy. org/modality/iontophoresis.
89. Herwadkar A and Banga AK: Peptide and protein transdermal drug delivery. Drug Discovery Today: Technologies 2012; 9(2).
90. Publisher BS: Transdermal Iontophoresis. Current Technologies to Increase the Transdermal Delivery of Drugs 2012; 41-52.
91. Barsness M, Davis SP and Etheredge R: Studies in drug transport vs. current in iontophoretic onychomycosis treatment. Conf Proc IEEE Eng Med Biol Soc. 2009; 289-94.
92. Nair AB, Kim HD and Davis SP: An *ex vivo* toe model used to assess applicators for the iontophoretic ungual delivery of terbinafine. Pharm Res. 2009; 26(9): 194-201.
93. Nair AB, Vaka SR and Murthy SN: Transungual delivery of terbinafine by iontophoresis in onychomycotic nails. Drug Dev Ind Pharm. 2011; 37(10): 1253-8.
94. Transport Pharmaceuticals. A study of skin/nail sensation and the pharmacokinetics of the uptake of terbinafine in the great toe nail and systemically following treatment with the electrokinetic transungual system (ETS)-terbinafine gel in healthy normal voluneteers 2009.

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