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 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. 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. 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. These are formulations which are pain free to administer and thus have high patient compliance and at the same time are cost effective.

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. Although the topical route is still restricted to narrow range of drugs, researches to include more drug is going on in this field. 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. 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. 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. 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. Iontophoresis is one of the physical methods. Various penetration techniques are shown below.

**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. It is still finding various other applications. Usually the electric potential applied to aid movement of drug is 0.5 mA/cm² 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. Iontophoresis is a second generation physical enhancement technique that has made a vital clinical impact due to its fast and localized delivery through skin the first and third generation being the application of transdermal patches and novel innovations to expand the extent of particles respectively. 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.

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

- Delivery of ionized and high molecular weight molecule can be made possible.
- Patient compliance can be improved by design that suit patient requirement such as continuous or pulsating delivery module.
- 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.
- Use of this technique makes it easier to terminate the delivery process.
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. Control span of activity. Lessen recurrence of dose. Self-organization is conceivable. An iontophoretic framework likewise comprises of an electronic control module which would take into account time differing of feedback controlled medication conveyance. 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. Iontophoretic conveyance averts tainting of medications repository for amplified timeframe. 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 iontophoresic 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. A controlled system to monitor the process is employed to check the proper working of all the components. A diagram showing the schematic representation of the instrument is given below.

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.

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. 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:

- 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.

\[
J(\text{ionto}) = J(\text{electric}) + J(\text{passive}) + J(\text{convective})
\]

Where:
- \(J(\text{ionto})\) = overall flux generated; \(J(\text{electric})\) = flux generated due to external electric field.
- \(J(\text{passive})\) = flux generated due to passive delivery through skin.
- \(J(\text{convective})\) = 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. 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. 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

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 can be easily used on the affected area.

**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.

**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.

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

**Hydrophillicity:** 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.

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

**TABLE 2: DRUGS USED IN IONTOPHORESIS**

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

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:

\[(\text{Current} \times \text{Treatment time})\]

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.

\[\text{Dose (Mass)} = \text{Dose (coulombs)} \times \text{Molecular Weight} / (9.632 \times 10000)\]

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 \textit{in vivo} conditions for the drug methyl salicylate on skin of human provides information about the following rank: Abdomen> Forearm> Instep> Heel> Planter. 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. These pathways are:

1. **Intercellular** - (paracellular) it is the pathway along the lamellar lipids in the corneocytes.
2. **Intracellular** - (transcellular) It is the pathway through the cells in the stratum corneum.
3. **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. 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.

The flip flop movement of polypeptide helices allocates a potential dependent pore formation in the stratum corneum. Intracellular transport of ions also occurs simultaneously with follicular transport.
but their contribution towards the total flux transport is likely small. 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.

**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\(^6^2\).

**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\(^6^3\).

**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\(^6^4\). 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\(^6^5, 6^6\). The suggested mechanism used in the treatment of hyperhidrosis: 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\(^6^8\).

**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\(^6^9\).

**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\(^6^9, 7^0\).

**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\(^7^1\).

**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\(^7^2\).

**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\(^7^3\). 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
- Trans scleral 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, conjunctival 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 recoloring 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 iontophoreric 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 \textit{in vitro}. There are currently two iontophoteric devices under clinical trials. Electro kinetic transungual system is a device under phase I clinical studies and power paper iontophotoric 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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