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IONTOPHORESIS: A NOVEL TECHNIQUE FOR TRANSDERMAL DRUG DELIVERY

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ABSTRACT

The delivery of drugs into systemic circulation via skin has generated much attention during the last decade. Transdermal therapeutic systems propound controlled release of active ingredients through the skin and into the systemic circulation in a predictive manner. Drugs administered through these systems escape first-pass metabolism and maintain a steady state scenario similar to a continuous intravenous infusion for up to several days. However, the excellent impervious nature of the skin offers the greatest challenge for successful delivery of drug molecules by utilizing the concepts of iontophoresis. The present review deals with the principles and the recent innovations in the field of iontophoretic drug delivery system together with factors affecting the system. This delivery system utilizes electric current as a driving force for permeation of ionic and non-ionic medications. The rationale behind using this technique is to reversibly alter the barrier properties of skin, which could possibly improve the penetration of drugs such as proteins, peptides and other macromolecules to increase the systemic delivery of high molecular weight compounds with controlled input kinetics and minimum inter-subject variability. Although iontophoresis seems to be an ideal candidate to overcome the limitations associated with the delivery of ionic drugs, further extrapolation of this technique is imperative for translational utility and mass human application.

KEYWORDS: Drug delivery, Translational research, Transdermal therapeutic system, Iontophoresis.

INTRODUCTION[1,2]

Iontophoresis (ionto – ion; phoresis – to transfer) is application of electric potential that maintains a constant electric current (0.5mA/cm^2 or less) across skin enhances delivery of ionized as well as unionized moieties for therapeutic purpose. Its principle based on like charges repel each other and unlike attract themselves.

In popular terms it is called "an injection without needle" In the past it has sometimes been called electromotive drug administration. This is localized, sterile, non invasive, convenient, painless and rapid method of delivering water soluble and ionized drug into layers of skin. The skin being a semipermeable membrane, allows small amount of drug molecule. Capability of this method is used to increase systemic delivery of high molecular weight compounds with controlled input kinetics also improved systemic bioavailability.

This technique provide predictable and extended duration of action and beneficial treatment for many skin disorders like hyperhydrosis and have positive effect on healing process, ensuring from bypassing first pass effect of metabolism. The highly lipophilic nature of skin restricts the permeation of hydrophilic, high molecular weight and charged compounds through the stratum corneum into the systemic circulation. The iontophoresis method was first described by Pivati in 1947. Galvani and Volta, two well-known scientists combined the knowledge that electricity can move different metal ions and that movements of ions produce electricity.

This method is different from Phonophoresis i.e. Ultrasound method which involves driving of ions across skin with therapeutic ultrasound. Iontophoresis repels drug ions through the skin and into underlying tissue. The use of iontophoresis for transdermal drug delivery has been successfully used by medical professionals for decades and continues to increase dramatically because of its advantages.

However, most therapeutic peptides or proteins are not delivered by the oral route, due to rapid degradation in the stomach and size-limited transport across the epithelium. The primary mode of administering macromolecules is therefore via injection which is not without limitations, such as the invasive nature of injections eliciting pain and lower acceptance/compliance by patients, in addition to the requirement for administration by a trained administrator. Rationally, the conventional routes of medication delivery have many

inherent limitations which could potentially be overcome by advanced drug delivery methodologies such as transdermal drug delivery (TDD).

- **TRANSDERMAL DRUG DELIVERY (TDD)[3,4]**

TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug initially penetrates through the stratum corneum and then passes through the deeper epidermis and dermis without drug accumulation in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation.

TDD has many advantages over other conventional routes of drug delivery. It can provide a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia. A large surface area of skin and ease of access allows many placement options on the skin for transdermal absorption. Furthermore, the pharmacokinetic profiles of drugs are more uniform with fewer peaks, thus minimizing the risk of toxic side effects. It can improve patient compliance due to the reduction of dosing frequencies and is also suitable for patients who are unconscious or vomiting, or those who rely on self-administration. TDD avoids pre-systemic metabolism, thus improving bioavailability.

With reference to the use of the skin as a novel site for vaccination strategies, this organ is known to be replete with dendritic cells in both the epidermal and dermal layers which play a central role in immune responses making TDD an attractive vaccination route for therapeutic proteins and peptides. The requirement for an inexpensive and non-invasive means of vaccination, especially in the developing world, has given rise to substantial research focused on the development of simple, needle-free systems such as TDD for vaccination purposes.

- **A BRIEF REVIEW OF SKIN STRUCTURE[5]**

Skin is the most accessible and largest organ of the body with a surface area of 1.7 m^2, compromising 16% of the total body mass of an average person. The main function of the skin is to provide a protective barrier between the body and the external environment against microorganisms, the permeation of ultraviolet (UV) radiation, chemicals, allergens and the loss of water.

Skin can be divided into three main regions

(1) The outermost layer, the epidermis, which contains the stratum corneum;

(2) The middle layer, the dermis and

(3) The inner most layer, the hypodermis (Figure 1).

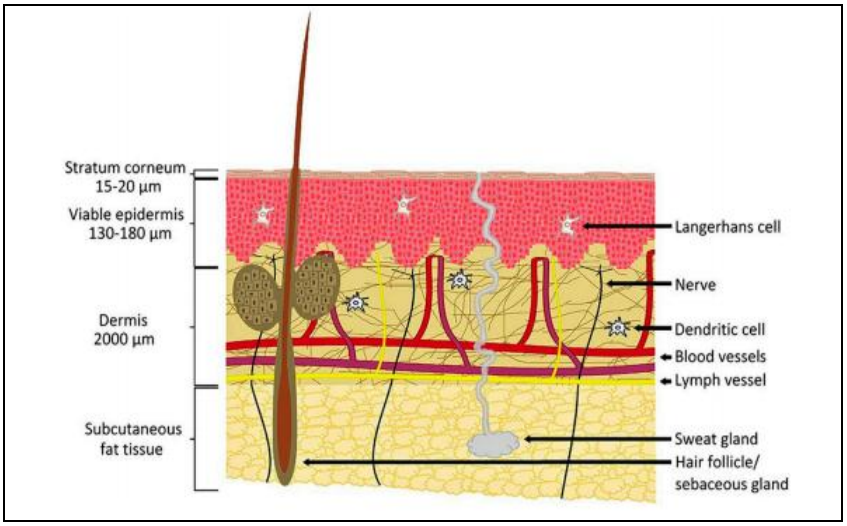

Figure 1: Anatomy of the skin.

1. Epidermis

The epidermis is the outermost layer of the skin and varies in thickness with approximately 0.8 mm on the palms of the hands and soles of the feet. It consists of multi-layered regions of epithelial cells and the viable epidermis is often referred to as the epidermal layers below the stratum corneum. The cellular content of the epidermis consists predominantly of keratinocytes (approximately 95% of cells), with other cells of the epidermal layers including melanocytes, Langerhans cells and merkel cells .The stratum corneum is the most superficial layer of the epidermis. It is in direct contact with the external environment and its barrier properties may be partly related to its very high density (1.4 g/cm^3 in the dry state) and its low hydration of 15%–20%. The cells of the stratum corneum are composed mainly of insoluble keratins (70%) and lipid (20%). Water in the stratum corneum is associated with keratin in the corneocytes.

2. Dermis

The dermis is approximately 2–3 mm thick and consists of collagenous (70%) and elastin fibres which give strength and elasticity to the skin. Blood vessels found in the dermis provide nutrients for both the dermis and epidermis. Nerves, macrophages and lymphatic vessels are also present in the dermis layer, as depicted in Figure 1.

3. Hypodermis

The hypodermis or subcutaneous layer is the deepest layer of the skin and consists of a network of fat cells. It is the contact layer between the skin and the underlying tissues of the body, such as muscles and bone. Therefore, the major functions of the hypodermis are protection against physical shock, heat insulation and support and conductance of the vascular and neural signals of the skin. Hypodermis-resident fat cells account for approximately 50% of the body's fat with the other predominant cells of the hypodermis consisting of fibroblasts and macrophages.

- **DRUG PENETRATION ROUTES[5,6]**

There are two possible routes of drug penetration across the intact skin, namely the transepidermal and transappendegeal pathways, which have been diagrammatically presented in Figure 2.

The transepidermal pathway involves the passage of molecules through the stratum corneum, an architecturally diverse, multi-layered and multi-cellular barrier. Transepidermal penetration can be termed intra- or inter-cellular. The intra-cellular route through corneocytes, terminally differentiated keratinocytes, allows the transport of hydrophilic or polar solutes.

Transport via inter-cellular spaces allows diffusion of lipophilic or non-polar solutes through the continuous lipid matrix.

The transappendegeal route involves the passage of molecules through sweat glands and across the hair follicles.

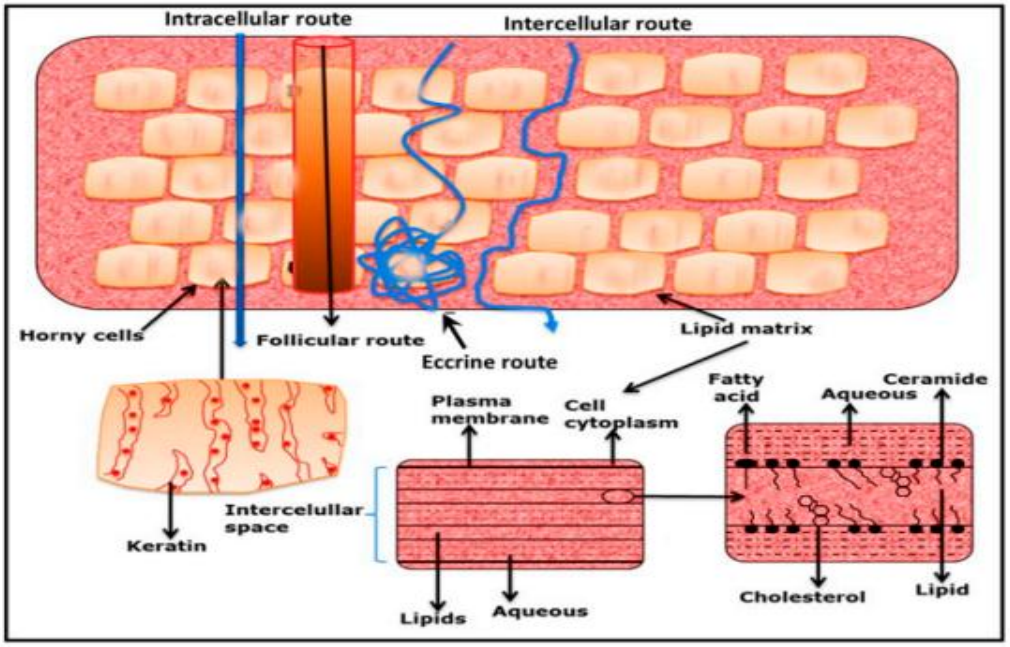

Figure 2: Possible drug penetration routes across human skin.

- **Techniques For Enhancement of Skin Permeabilisation**[6,7,8]

Technologies used to modify the barrier properties of the stratum corneum can be divided into passive/chemical or active/physical methodologies (Figure 3). Passive methods include the influencing of drug and vehicle interactions and optimization of formulation, in order to modify the stratum corneum structure. Passive methods are relatively easy to incorporate into transdermal patches such as chemical enhancers and emulsions. However, the main drawback of passive methods may be a lag time in drug release incurred with obvious negative influence on rapid onset drugs, such as insulin.

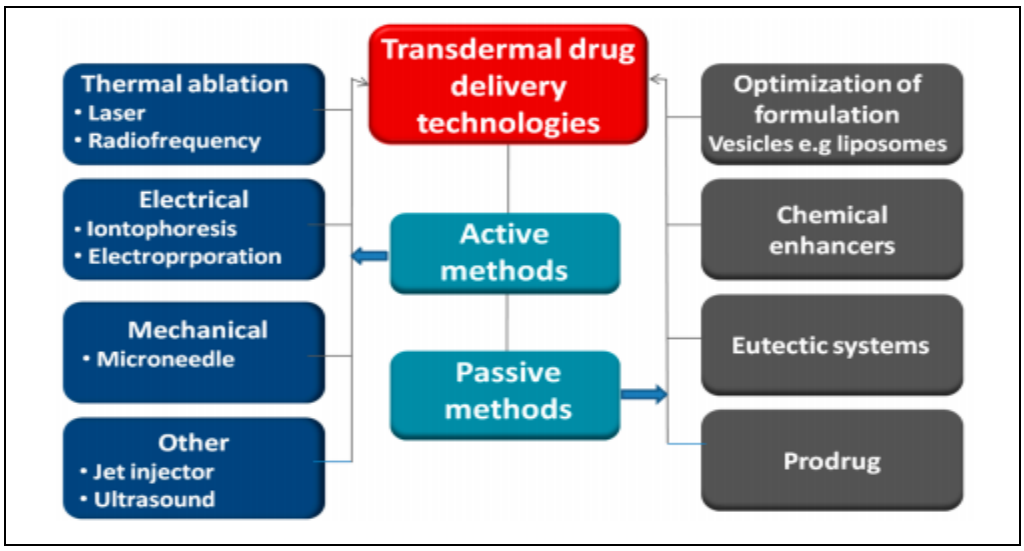

Figure 3: Approaches for enhancing drug transport across the skin.

- **Principles of Iontophoresis**[9,10]

The Iontophoretic technique is based on the general principle that like charges repels each other and opposite charge attract. Thus during iontophoresis, if delivery of positively charged drug is desired, the charged drug is dissolved in the electrolyte surroundings the electrode of similar polarity, i.e. anode. An application of electromotive force the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body. Communication between the electrodes along the surface of the skin has been shown to be negligible. When cathode is placed in the donor compartment of the Franz diffusion cell to enhance the flux of an anion, it is termed cathode iontophoresis and for anodal iontophoresis the situation would be reversed. If any neutral molecules are present at the anode at this time the can be transported through the skin along with the water. Such water movement often results in pore shrinkage at the anode and pore swelling at cathode. Electro-migration of ions during iontophoresis causes convective solvent motion and this solvent motion in turn „drags" neutral or even charged molecules along with it. This process is termed as electro-osmosis. At pH values above 4, the skin is negatively charged; implying that positively charged moieties like Na+ will be more easily transported as they attempt to neutralize the charge in the skin to maintain electro neutrality. Thus the movement of ions under physiological conditions is from the anode to the cathode. For loss of each cation (sodium ion in this case) from the electrode in this process, a counter ion, i.e. an anion, Cl − moves in the opposite direction from the cathode to the anode.

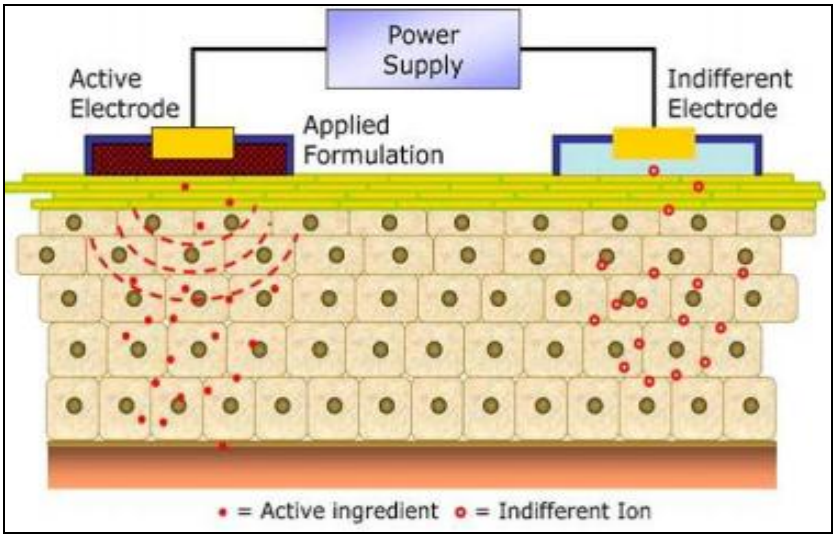

Figure 4 Principles of Iontophoresis.

- **MERITS**[8,9]

→ It is non-invasive technique could serves as substitute for chemical enhancers.

→ Eliminate problems like toxicity, adverse reaction and formulation related problems.

→ Prevent variation in the absorption of TDDS.

→ Eliminate chance of over and under dosing by continuous delivery of drug programmed at the required therapeutic rate.

→ Provide predictable and extended duration of action.

→ Reduce frequency of drug.

→ Self administration is possible.

→ Provide simplified therapeutic regimen, leading to better compliances.

→ Permit rapid termination of the modification.

→ It may permit lower quantities of drug compared to use in TDDS.

→ TDDS of many ionized drug at therapeutic levels was precluded by their slow rate of diffusion under a concentration graduation, but iontophoresis enhanced flux of ionic drugs across skin under electrical potential gradient

→ It is important in systemic delivery of peptide/protein based pharmaceuticals, which are very potent, extremely short acting and often require delivery in a circadian pattern to simulate physiological rhythm, eg. Thyrotropine releasing hormone, somatotropine, tissue plasminogen activators, interferons, enkaphaline, etc.

→ Provide predictable and extended duration of action.

→ A constant current iontophoretic system automatically adjusts the magnitude of the electric potential across skin which is directly proportional to rate of drug delivery.

→ An iontophoretic system also consists of a electronic control module which would allow for time varying of free-back controlled drug delivery Iontophoresis turned over control of local anesthesia delivery in reducing the pain of needle insertion for local anesthesia.

→ By minimizing the side effects, lowering the complexity of treatment and removing the need for a care to action, iontophoretic delivery improve adherence to therapy for the control of hypertension

→ Iontophoretic delivery prevents contamination of drugs reservoir for extended period of time.

- **Demerits**[9,10]

→ Iontophoretic delivery is limited clinically to those applications for which a brief drug Delivery period is adequate.

→ An excessive current density usually results in pain burns are caused by electrolyte changes within the tissue.

→ The safe current density varies with the size of electrodes.

→ The high current density and time of application would generate extreme pH, resulting in a chemical burn. This change in pH may cause the sweat duct plugging perhaps precipitate.

→ Protein in the ducts or hyperhydrate the tissue surrounding the ducts.

→ Electric shocks may cause by high current density at the skin surface.

→ Possibility of cardiac arrest due to excessive current passing through heart.

→ Ionic form of drug in sufficient concentration is necessary for iontophoretic delivery.

→ High molecular weight compounds results in a very uncertain rate of delivery.

- **Drug Selection In Iontophoresis**[8]

✓ The drug candidates should be storable in liquid or dry form in the patch and should be stable.

✓ It should be soluble in aqueous media and be charged.

✓ The isoelectric point should be in the range of smaller than 4 or greater than 7.4.

✓ The iontophoretic device should deliver the drug in following manner 20-50 mg drug/day of molecular weight of 300 Da, 2-5 mg drug/day of molecular weight of 1000 Da and 100 µg drug/day of molecular weight of 5000 Da.

- **Challenges In Delivery**[10]

The main goals in iontophoresis that should be met are delivery of appropriate dose throughout the dosing interval, ensure system is safe, adhere effectively and is not irritating. The third objective is to develop a product that is elegant, cost effective and acceptable by patients. Proper planning is required to achieve these objectives. Sometimes, there is pH change across skin layers and the charge on molecule of interest changes as it travels through the skin and as a result drug may not traverse the skin. Extensive preformulation is required to understand the physical and chemical characteristics of the drugs.The cost of the device could be reduced by using the reusable type of systems in which hydrogel pad can be

replaced with other. Also microprocessor from disposable device can be used for another system to keep the cost low.

- **How to define dose in iontophoresis.**[11]

For iontophoresis the dosage is measured in milliampminutes because it is based on the current and that is the type of dosage. An iontophoresis treatment is set to deliver a current (For e.g. 2 mA) and patient is treated for short period of time (For e.g. 10 min session or 20 mA min dosage). Typically, solutions that are placed on electrode are about 1.5 mL in volume and range in concentration from 2-5%. The administration can be continuous or bolus using microprocessor and appropriate circuitry. As current controls the amount of drug delivered, administration can be programmed to provide the bolus dose immediately and then a slow maintenance dose over a period of time.

- **Types of Iontophoretic System**[10,12]

The system of drug delivery via iontophoresis can be classified in accordance to the modification and improvement done in this system which allows the uniform and predictive drug release in an effective manner.

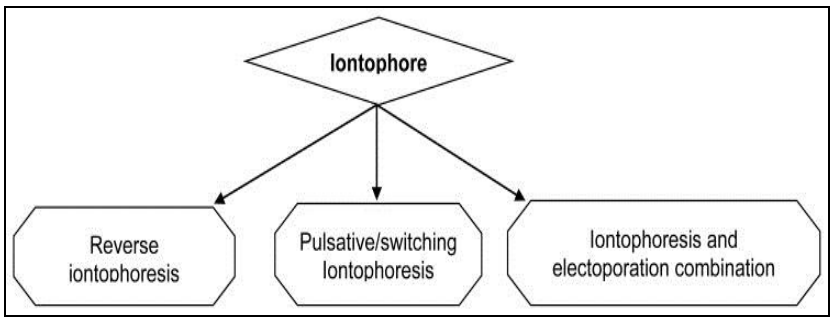

Figure 5: Various types of iontophoretic system.

➢ **Reverse iontophoresis**

Reverse iontophoresis, a technique in which low electric current is applied to draw intestinal fluid through the skin, is widely applied these days in devices meant for diagnostic application. This provides a convenient and non-invasive method for sampling of body fluids so as to permit simultaneous measurement of the desired substance in the body fluid and thus to monitor them efficiently. The reverse iontophoretic process applies to continuously monitor the glucose level in the blood for e.g. Glucowatch®, which is a system that provides a needleless means of monitoring blood glucose levels in diabetic patients and uses an electrical signal which is proportional to the amount of glucose in the extracellular fluid. This

provides a feasible method for rapid, linear extraction of phenylalanine and for easy detection (by instruments like biosensors) of monitoring diseases like phenylketonuria. This technique not only provides non-invasive sampling but also provides filtered samples free from large molecules with ease of operation. However, this technique is useful for less tedious sampling. For it to be successful, it needs a very sensitive analytical method since the amount extracted is very low. For e.g. Caffeine, theophyline; lithium; phenytoin are successfully tried using this approach.

➢ ***Pulsatile/switching iontophoresis***

Many studies have been conducted where instead of using constant DC iontophoresis, DC in the form of short pulses have been used.

➢ ***Iontophoresis and electoporation combination***

Iontophoresis can also be combined with other skin penetration enhancing techniques like electoporation, which involves the application of high voltage (> 100 V) pulses for short duration (μs-ms) to increase the permeability through the skin. Electoporation is applied before iontophoresis, which causes the creation of permeablized skin because of exposure to high pulses voltage. Thus, when applied after electoporation, iontophoresis helps in extending the permeablized state of the skin, resulting in the rapid onset (which is a drawback of iontophoresis alone) and sometimes increased flux. The increased transport by electoporation caused by creation of electro pores as well as local field induced electrophoretic drift. Fang et al., studied the effect of electoporation on the delivery of buprenorphine and showed that on application of 300 V or 500 V pulses increased the buprenorphine flux by several folds over passive transport of it; e.g. drugs like Salmon calcitonin (SCT) and PTH combination; Tacrine hydrochloride have been successfully tried using this approach.

- **Factors Affecting Iontophoretic Delivery Of The Drug**[11,12,13]

Name of the factors			
Physiochemical Properties	**Drug formulation**	**Experimental factors**	**Biological factors**
Molecular size	pH	Current strength	Intra and inter subject variability
Molecular weight	Ionic strength	Current density	Regional blood flow
Charge	Presence of co-ions	Pulsed current	Skin pH
Polarity		Duration of application	Condition of skin
Concentration		Electrode materials	

A. PHYSIOCHEMICAL PROPERTIES

Molecular size and molecular weight

The molecular size of the solute is a major factor governing its feasibility for iontophoretic delivery and hence the amount transported. When the iontophoretic delivery of carboxylate ions was studied, flux for acetate was found to be more than that of hexanoate and dodecanoate. This suggests that smaller and more hydrophilic ions are transported at a faster rate than larger ions, the permeability coefficients in positively charged, negatively charged and uncharged solutes across human skin are a function of molecular size. When the molecular size increases, the permeability coefficient decreases. Many studies correlating flux as a function of molecular weight have been conducted and it was concluded that for electro repulsive iontophoresis, when all other conditions were kept constant, transport of compounds decreased with increase in molecular weight (chloride> amino acid >nucleotide > tripeptide >insulin).

Charge

Charge on a molecule is an important physicochemical property governing iontophoretic transport, since the sign of the charge determines the mechanism by which iontophoresis will proceed e.g., electrorepulsion and electroosmosis. Although the transport of cations has been shown to be better than anions for amino acids and peptides, this however is not so simple because an increase in charge will require pH to be decreased, which in turn shall directly decrease the electroosmosis and electrotransport process. An increased positive charge on peptide, cause it to bind tightly to the membrane creating a reservoir which in turn can decrease the rate at which the steady state flux will be achieved.

Polarity

Generally, the compounds which are hydrophilic are considered ideal candidates for optimum flux e.g., nalbuphine and its ester showed an increased flux as the lipophilicity of the compound decreased.

Concentration

Concentration of drug is one of the most important factors affecting iontophoretic process. The effect of the concentration has been studied on a number of drugs. An increase in concentration was shown to increase the apparent steady state flux of a number of drugs e.g., metoprolol, diclofenac sodium, rotigotine. All these drugs showed a proportional increase in flux with an increase in concentration. The concentration dependent iontophoretic delivery

has not been fully investigated, some of the authors reported that as the concentration of drugs viz. acetate ions and hydromorphones, increase in reservoir system then permeation of drug also increases.

B. DRUG FORMULATION

pH

pH is an important factor governing the iontophoretic delivery of drugs, this affects iontophoresis in two ways. The pH of the donor solution influences the pH of the skin and thus makes the skin a permselective membrane especially if the pH of the skin rises above 4. This causes the carboxylic acid moieties in the skin to become ionized and then the anodal iontophoresis promotes the permeation of cationic drugs. The pH of the donor solution also affects the ionization of the drug itself. Thus a weakly basic drug will be ionized to a lower extent at pH higher than its pKa and will not permeate by electromigration in presence of iontophoresis. The drug will be more dependent on electro-osmosis to travel across the skin.

Ionic strength

The ionic strength of a drug delivery system is directly related to the iontophoretic permeation of drugs. Some authors reported that increasingly the ionic strength of the system decreases the permeation rate of drug and has no significant effect on penetration up to the 0.5 V. Many peptides widely studied for ionic strength showed a higher flux occurring at low electrolyte concentration.

Presence of co-ions

An ion of equal charge but of different type is referred as a co-ion. The buffering agents used to maintain pH of the donor medium is a source of co-ions. These co-ions are generally more mobile and smaller in size than the drug ions. The presence of a co-ion (ion with the similar charge as the drug) results in competition between the drug and the co-ion, a reduction of the fraction of the current carried by the drug and thus a reduction in the transdermal iontophoretic flux of the drug. Nugroho et al. compared the transdermal iontophoretic permeation of rotigotine in presence of three different co-ions: Na+ , tetra ethyl ammonium (TEA+) or tetra butyl ammonium (TBA+) at pH 5 and 6. The iontophoretic flux of rotigotine was lower in presence of Na+ as compared to TEA+ and TBAC which can be attributed to the higher mobility of the sodium ion due to its lower molecular weight. Replacing Na+ by the larger coion TEA+ resulted in an increase of the rotigotine flux both at pH 5 and 6.

C. EXPERIMENTAL FACTORS

Current strength

Current can easily be controlled by the use of electronics; it is a convenient mean to control delivery of drugs to the body. There is a linear relation between the observed fluxes of a 1-cm^2; the current is limited to 1 mA due to patient comfort considerations. This current should not be applied for more than 3 min because of local skin irritation and burns. With increasing current, the risk of non specific vascular reactions (vasodilatation) increased. In general, 0.5 mA/cm^2 is often stated to be the maximum iontophoretic current which should be used on human beings.

Current density

Current density is the quantity of current delivered per unit surface area. The following criteria should be considered in selecting proper current densities for IP. The current should be sufficiently high to provide a desired drug delivery rate. It should not produce harmful effects to the skin. There should be a quantitative relationship between the applied current. The drug should be electrochemically stable.

Pulsed current

The continuous use of direct current (DC), proportional to time, can reduce the iontophoretic flux because of its polarization effect on the skin. This can be overcome by the use of pulsed DC which is a direct current delivered in a periodic manner. During “off stage” the skin gets depolarized and returns to the initial polarized state. However, Bagniefski and Burnett showed that enhanced skin depolarization can decrease the efficiency of drug transport, if the frequency of pulsed current is very high.

Duration of application

The transport of drug delivery depends on the duration of current applied in iontophoretic drug delivery.The iontophoretic penetration of drug linearly increased with increasing application time.The skin permeation of arginine vasopressin achieves higher plateau rate and in case of insulin delivery, 2-3 fold reduced the blood glucose levels with increase in duration of iontophoretic application.

Electrode materials

The electrode materials used for iontophoretic delivery are to be harmless to the body and sufficiently flexible to apply closely to the body surface. The most common electrodes are

aluminum foil, platinum and silver/silver chloride electrodes used for iontophoretic drug delivery. The type of electrodes used also affect the iontophoretic delivery. Electrodes Ag/AgCl are the most preferred as they resist the changes in pH which are generally seen during the use of platinum or zinc/zinc chloride electrodes. The following reactions typically occur at the anode.

$$Ag+Cl- -AgCl+e$$

The electron is released to the circuit and insoluble AgCl precipitates at the anode surface. In the case of other metals like platinum, the chloride ion at the anode will be converted to Cl_2 which will in turn react with water to generate hydronium ions. These then migrate to the donor solution and compete with similarcharged drug ions and being highly mobile enter the skin thus reducing drug transport and simultaneously causing skin irritation. The positioning of electrodes in reservoir depends on the charge of the active drug. The distribution of drug within the skin depends on the size and position of electrodes. They are usually selected according to individuals needs. Larger electrode areas introduce the greater amounts of drug but lesser current density is tolerated to the skin in a non-linear manner. Metal electrodes touching to the skin produce burns with much lower current in composition to padded electrodes. A loose contact between the padded electrode and skin also produce burn due to uneven distribution of current. The safe current density varies with the size of electrodes.

D. BIOLOGICAL FACTORS

Intra and inter subject variability

Iontophoresis reduces intra and inter-subject variability in the delivery rate. This is an inherent disadvantage with the passive absorption technique. Experiments in vivo iontophoretic give support for clinical findings that there are small differences in the flux rate following transdermal iontophoresis between males and females, as well as between hairy and hairless skin.

Regional blood flow

During iontophoresis, the dermal blood supply determines the systemic and underlying tissue solute absorption. Blood supply however, does not appear to affect the drug penetration fluxes through the epidermis during iontophoretic delivery. Cross and Roberts showed that solute in the upper layer of the skin following iontophoresis was comparable in anaesthetized rats and sacrificed rats. It can thus be presumed that the blood did not affect the penetration through the epidermis since the latter has no blood supply.

Condition of skin

In iontophoresis, skin condition also affects the penetrating properties of permeant. Roberts et al., studied the in vivo passive diffusion of methyl salicylate using skin from different areas of human body and observed the following rank order: abdomen> forearm> instep> heel> planter, for all subjects.

- **APPLICATIONS OF IONTOPHORESIS**[13,14,15]

A. Topical delivery

The ability to control the delivery rates of drugs by changes in current makes iontophoresis an attractive technique to use. Yamashita et al. studied the efficacy of iontophoretic delivery of calcium for treating hydrofluoric acid-induced burns.

B. Treatment of hyperhydrosis

Hyperhydrosis (also called hyperhidrosis) is a condition that most often results in excessive sweating in the hands and feet. Tap water iontophoresis is one of the most popular treatments used in this condition. The procedure uses a mild electrical current that is passed through tap water to temporarily shut off sweat glands. According to one hypothesis, iontophoresis may induce hyperkeratosis of the sweat pores and obstruct sweat flow and secretion (although no plugging of the pores has been found. Successful induction of hypohydrosis by tap-water iontophoresis requires the application of 15–20 mA to each palm or sole for 30 min per session for 10 consecutive days, followed by one or two maintenance sessions per week.

C. Diagnostic applications

Iontophoretic application of the drug pilocarpine produces intense sweating, allowing sufficient amounts of sweat to be collected and analyzed. This is now accepted as the primary test in the diagnosis of cystic fibrosis. Other drugs such as phenytoin, lithium, caffeine and theophylline are used for the diagnostic application.

D. Ophthalmology

Iontophoresis has been used experimentally to deliver antibiotics into the eye. The principal disadvantage of this technique is the time required for direct contact of the electrode with the eye.

E. Otorhinolaryngology

Iontophoresis is a preferred method for obtaining anesthesia of the tympanic membrane prior to simple surgical procedures involving that structure. Iontophoresis of zinc has also been used for the treatment of patients with allergic rhinitis.

F. Dentistry

Beginning in the late 19th century, dentists applied local anesthetics to their patients prior to oral surgical procedures. Gangarosa described the use of iontophoresis for three basic applications in dentistry:-

1) Treatment of hypersensitive dentin (e.g. - in teeth sensitive to air and cold liquids) using negatively charged fluoride ions;
2) Treatment of oral ulcers ("canker sores") and herpes orolabialis lesions ("fever blisters") using negatively charged corticosteroids and antiviral drugs, respectively; and
3) The application of local anesthetics to produce profound topical anesthesia, as is done in some physical therapy applications.

G. Non-invasive monitoring of glucose

Electro osmotic flow generated by application of low Level current has been used for extraction of glucose through the skin. As the direction of glucose flow is in the opposite direction (in outward direction in skin) to conventional iontophoresis, it is called reverse iontophoresis. This property in combination with insitu glucose sensors has been used in Gluco Watchw Biographer This device allows noninvasive extraction glucose across the skin, allowing a diabetic‟s glycemia to be evaluated every 10 min over several hours.

H. Peptide delivery

This is the most promising applications of iontophoretic transdermal delivery. Transdermal delivery itself offers the advantages of bypassing first pass metabolism and gastrointestinal degradation as well as patient compliance over the existing oral and parenteral routes of administration for peptide delivery. An additional advantage that it offers specifically for proteins and peptides is the avoidance of strong proteolytic conditions as found in the gastrointestinal tract. The delivery of oligopeptide, vasopressin can be done by ionto therapeutic system.

I. Dermatology

Iontophoresis has many uses in the field of dermatology. Except for the use of lidocaine for anaesthesia and the treatment of patients with hyperhidrosis, most uses of iontophoresis in dermatology have largely been abandoned. Iontophoresis with tap water or anticholinergic compounds has been used for the treatment of patients with hyperhidrosis of the palms, feet, and axillae.

- **VARIOUS SYNERGISTIC APPROACHES WITH IONTOPHORESIS[14,15]**

1. Iontophoresis in conjunction with electroporation

Iontophoresis and electroporation are both methods of electrically assisted transdermal drug delivery. Iontophoresis is more commonly used to deliver lipophilic small molecular weight drugs, while electroporation seems more effective for the delivery of some macromolecules such as antisense oligonucleotides, peptides and proteins. Drug delivery with iontophoresis and electroporation are thought to utilize different penetration pathways Fluorescent microscopy and laser scanning confocal microscopy were used to visualize the FITC labeled phosphorothioate oligonucleotides transport at the tissue and cell level respectively in hairless rat skin after iontophoresis or electroporation. In the SC the transportation pathways for FITC labeled phosphorothioate oligonucleotides were more transcellular during electroporation and paracellular during iontophoresis .The practical application of combining electroporation with iontophoresis is still in its initial feasibility stage much like the commercial development of electroporation devices for transdermal delivery of drugs.

2. Iontophoresis in conjunction with chemical enhancers

Although the use of iontophoresis results in much higher drug delivery if compared with conventional passive transdermal delivery, it still has limitations as a technique. Chemical enhancers can be used in combination with iontophoresis to achieve even higher drug penetration. In addition to increasing transdermal transport, a combination of chemical enhancers and electrically assisted delivery should also reduce the side effects such as irritation caused by high concentration of enhancers or stronger electric forces. The combined effects of enhancers and electrically assisted delivery depend on the physico-chemical properties of the penetrant, enhancer and their behavior under the influence of an electric field. Occasionally, the use of chemical enhancers was reported to result in reduced flux compared with using iontophoresis alone. However, more often synergistic effects have been reported such as those with fatty acids, and terpenes and others.

3. Iontophoresis conjunction with sonophoresis

Synergy between low-frequency ultrasound and iontophoresis would be expected since the techniques both enhance transdermal transport although through different mechanisms. As a matter of fact, the disruption of SC lipid bilayer by the application of ultrasound can be utilized by further use of iontophoresis to increase transdermal drug transport to a greater degree. This combination has been found to enhance transdermal transport better than any of the single treatments alone. Iontophoresis combined with low frequency ultrasound was used in the transdermal delivery of sodium nonivamide acetate (SNA). Pretreatment of the skin with low frequency ultrasound (0.2 W/cm^2, 2 h) alone did not increase the skin permeation of SNA. The combination of iontophoresis (0.5 mA/cm^2) and sonophoresis increased transdermal SNA transport more than iontophoresis alone.

4. Iontophoresis in conjunction with microneedles

Few studies have reported the combination of iontophoresis with microneedle technologies. This combination may provide the possibility of macromolecule transdermal delivery with precise electronic control. Lin et al. designed a Macrofluxw® and iontophoresis combined transdermal ISIS 2302. The Macrofluxw® array, 2 cm^2 , had a microprojection density of 240/cm^2 and a needle length of 430 µm. Macrofluxw® and iontophoresis combined system was made by assembling the Macrofluxw array, a drug reservoir, a membrane, a conductive gel and the iontophoretic electrode.

5. Iontophoresis in conjunction with ion-exchange materials

For this combined technique, experimentally the ion exchange materials were initially immersed into drug solution for 3 h to overnight. Afterward, such a drug-loaded device (e.g. disc, a bundle of ion exchange fibers or hydrogel filled with ion exchange resins) was transferred to the donor part of a diffusion cell for in vitro or in vivo tests. The successful in vivo delivery of therapeutic dosage of tacrine, an anti-Alzheimer's disease agent.

• FUTURE PROSPECT

There is too much to look forward for iontophoretic drug delivery system. There is enormous opportunity for iontophoresis because many products present in market are very difficult to deliver by passive diffusion. Also the onset of action of such products is very slow as compared to active diffusion and takes considerable time until therapeutic dose is reached. The crucial to the success of iontophoresis is to develop products that are cost effective to the

consumer. Circus is exploring the use of nanotechnology in various areas of drug delivery and is capable of delivering technology to transdermal delivery to improve the skin permeation. Future trends for transdermal technology will include delivery of multiple drugs from the same patch and delivery of new chemical entities that will require new adhesives with even broader formulating capabilities. A number of researchers are investigating iontophoresis for gene delivery. Other important near-term applications include neurology, women's health and dermatology.

- **CONCLUSION**

Iontophoresis is one of the more promising methods to enhance delivery of drugs with poor permeation profile through the skin. Iontophoresis dramatically enhances both the rate of release and extent of penetration of the salt form of the drugs. Without iontophoresis, such charged species are not able to penetrate the skin due to lipophilic nature of the skin. Iontophoresis is gaining wide popularity as it provides non-invasive and convenient means of systemic administration of drugs with poor bioavailability profile, short half life and multiple dosing schedules. Iontophoresis, in comparison to oral route, definitely provides benefits of improved efficacy and reduction in adverse effects. It is believed to be practical alternative to parenteral therapy. The major advantages of iontophoretic drug delivery system are rate of drug input can be controlled and optimized. Thus, iontophoresis may become an important alternative method of drug delivery in the near future.

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