

IONTOPHORESIS IN DRUG DELIVERY: HISTORY AND APPLICATION

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Summary

The composition and architecture of the stratum corneum render it a formidable barrier to the topical and transdermal administration of therapeutic agents. The physicochemical constraints severely limit the number of molecules that can be considered as realistic candidates for transdermal delivery. Iontophoresis provides a mechanism to enhance the penetration of hydrophilic and charged molecules across the skin. Iontophoresis is a novel drug delivery system designed to improve the delivery rate of compounds. The technique generates an electrical potential gradient that facilitates the movement of solute ions across the membrane. Iontophoresis has been used with greatest success in therapy of hyperhidrosis. The potential of iontophoresis for systemic delivery is being rediscovered, and the technique has been observed to be particularly effective for ionic drugs. It also enhances transdermal permeation of neutral compounds by the process of electroosmosis. The recent enthusiasm for iontophoresis may also be attributed to successful production of therapeutically active protein and peptide drugs by employing recombinant DNA technology. Because of their charged nature and relatively large molecular size, iontophoresis may provide means for their effective delivery. This review discusses the basic principles and applications of iontophoresis in dermatology, ophthalmology, otolaryngology, and dentistry. In addition, the systemic applications of iontophoresis with emphasis on protein and peptide delivery are reviewed.

Key Words: Transdermal, Electrically-assisted delivery; Iontophoresis; Non-invasive; Topical; Transport mechanisms

INTRODUCTION¹⁻³

Trans-dermal administration of drug is assuming an important place in modern drug therapy. It is used for non-ionized drugs required in a small dosage. Transdermal administration can be passive or facilitated. In passive administration, the non-ionized drug traverses the skin through the stratum corneum. The skin, being a semi-permeable membrane, allows only a small amount of any drug molecule to passively penetrate the skin. Ionized drugs do not easily penetrate this barrier and are not suitable for routine trans-dermal delivery unless an external source of energy is provided to drive the drug across the skin. Facilitated diffusion can utilize either ultrasound (phonophoresis) or electrical (iontophoresis) energy. In iontophoresis, this external source of energy is in the form of an applied direct electrical current.

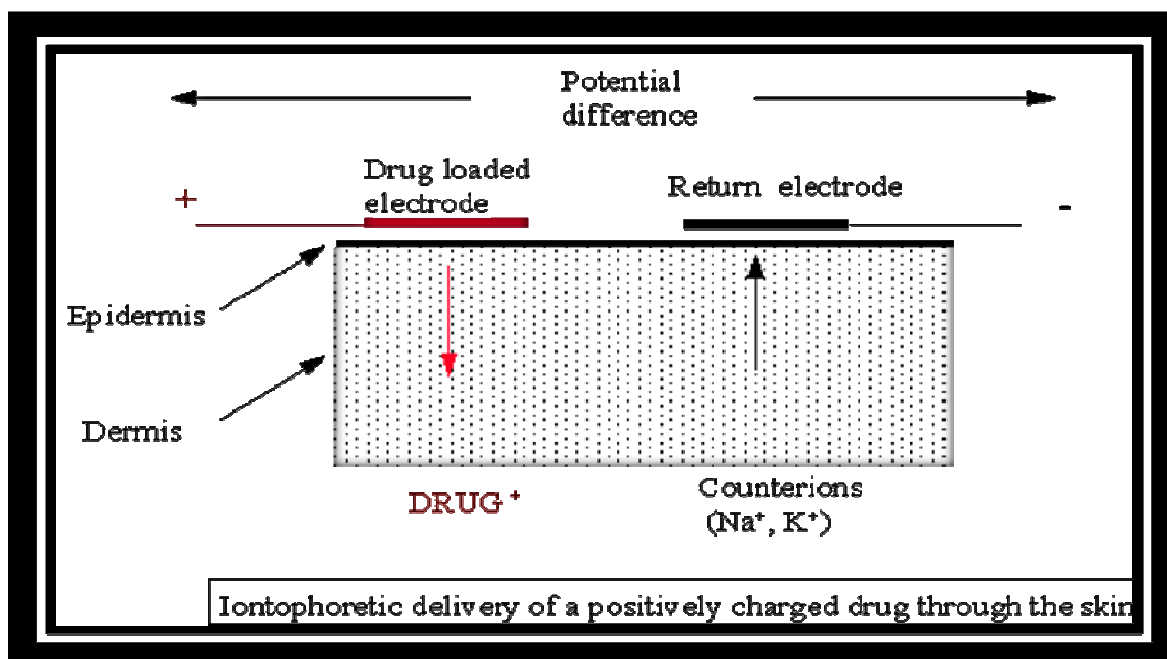
"Iontophoresis is a process of transportation of ionic molecules into the tissues by passage of electric current through the electrolyte solution containing the ionic molecules using a suitable electrode polarity." This means it would involve an electromotive force. It is a technique used to enhance the absorption of drugs across biological tissues such as the skin. Iontophoresis is the method where the movements of ions across a membrane enhanced using an externally applied potential difference. When the membrane under consideration is skin, the method is called transdermal iontophoresis.

The benefits of using transdermal drug delivery include:

- 1) Improved systemic bioavailability resulting from bypassing the first metabolism.
- 2) Variables due to oral administration, such as pH, the presence of food or enzymes and transit times can all be eliminated.

In the development of new transdermal drug delivery devices the aim is to obtain controlled, predictable and reproducible release of drugs into the blood stream of the patient.

The transdermal device acts as a drug reservoir and controls the rate of drug transfer. When the transdermal drug flux is controlled by the device instead of the skin, delivery of the drug is more reproducible leading to smaller inter and intrasubject variations, since the drug release from the device can be controlled accurately than the permeability of the skin. Due to this reason, Iontophoresis drug delivery plays remarkably important role in drug delivery to achieve better therapeutic effect while minimizing side effects associated with conventional drug delivery. The concept of drug delivery through the skin for systemic indications is now widely accepted. However, the number of drugs which may be delivered by the transdermal route is limited by the barrier properties of the skin. Conventional transdermal therapy is limited to small, potent and lipophilic drugs. Iontophoresis is one strategy devised to facilitate transdermal drug delivery. Iontophoresis may be defined as the facilitated movement of ions across a membrane, e.g. the skin. In order to deliver a positively charged drug across the skin, a solution of, for example, a cationic drug is placed at the positive electrode where it is repelled and then attracted towards a negative electrode place elsewhere on the body. Delivery of positively charged compounds is generally easier than negatively charged compounds as the skin itself possesses a net negative charge.



Although drugs may be delivered iontophoretically across the skin to exert a local effect, e.g. anaesthesia, current iontophoresis research is primarily focused on systemic drug delivery. Iontophoresis is a non-invasive drug delivery system with no trauma or risk of infection and is therefore a useful alternative to drug administration by injection.

The major commercial iontophoretic electrode, trans-Q^a, is designed such that charge is delivered to a hydrogel pad loaded with a drug solution. The hydrogel is moistened with a small volume of a previously prepared drug solution, squeezing the pad firmly several times, and allowing 60 seconds for complete hydration to take place. This procedure is obviously prone to error since the medication must be prepared correctly at the point of use and the gel pad must also be fully hydrated.

Work is ongoing at the BEST Centre in the School of Pharmacy, QUB to develop novel, bioadhesive, drug-containing electrodes for use in iontophoretic drug delivery. The design of the electrode overcomes many of the problems associated with present iontophoretic electrode designs. It is envisaged that this novel electrode may be used as a generic iontophoretic drug delivery system for a wide range of charged drugs.

In parallel with this research, the BEST Centre at QUB is currently designing a system for the detection of bacterial biofilm formation. Bacteria have a natural tendency to adhere to surfaces.

Following adhesion bacteria replicate and then secrete and become encapsulated within exopolymeric materials to form a microbial biofilm. Formation of microbial biofilm on surfaces causes problems in the food and energy industries. In the brewing industry, contamination of 'python' tubing can cause fouling of beer, whilst biofilm formation on pipelines reduces heat transfer efficiency. The use of electrodes that will detect biofilm formation on inert surfaces will ensure greater economic efficiency for industrial processes as appropriate cleaning processes may be initiated prior to the establishment of a mature biofilm. For the pharmaceutical industry, in particular, there are benefits associated with the validation of cleaning processes, an important part of pharmaceutical good manufacturing practice.

HISTORY OF TRANSDERMAL DELIVERY SYSTEM³

The first proposal for the use of electric current in the drug delivery dates from the mid 18th century. Serious progress was made in the 19th century notably by Benjamin Ward Richardson (1828-1896), Hermann Munk (1839-1912), William James Morton (1846-1920), Stephen Leduc (1853-1939) and Fritz Frankenhauser (born 1868). Administration of metal ions as well as alkaloids was tried at that time. Until the early 20th century, current medicated drug delivery was known as “cataphoresis”. Frankenhauser is said to have introduced the term “iontophoresis” before 1908. Recently researchers talk about “electrically-assisted transdermal drug delivery”. The technique was never widely adopted but always proved useful to some extent in solving particular drug delivery problems.

Twenty three years ago, the first transdermal drug delivery system was introduced in the US making a historic breakthrough, holding the promise that new compounds could be delivered in a safe, convenient way through this skin. And yet, during the last two decades, the commercial success of transdermal delivery has been slow to develop. But, as a spate of newer products and technologies move towards the market place, transdermal drug delivery seems to have arrived.

America’s first commercially marketed transdermal patch used a passive mode of drug delivery that permitted the drug to diffuse through the avascular dermis to the deep dermis, allowing local action or penetration to the capillaries for a systemic effect. But these passive systems had limitations. This approach depended on the drug’s properties to facilitate transport through the skin by using a simple concentration gradient as a driving force. Also, few drugs were available with the right physicochemical properties to make good candidates for transport through the skin. Even with these limitations, passive transdermal patches are experienced ever- increasing acceptance today.

While passive transdermal technology grows in popularity, all the available transdermal delivery systems use passive technology. Passive technology has always depended on the physicochemical properties of the drug candidate, large molecule drugs, such as, proteins and peptides, could not be considered. But, advances in the research have led to a better understanding of the physiology of the skin and more familiarity with the drug transport characteristics.

OVERVIEW OF STRUCTURE OF SKIN⁴

The skin has several layers. The overlaying outer layer is called epidermis; the layer below epidermis is called dermis. The dermis contains a network of blood vessels, hair follicle, sweat gland & sebaceous gland. Beneath the dermis are subcutaneous fatty tissues. Bulbs of hair project into these fatty tissues.

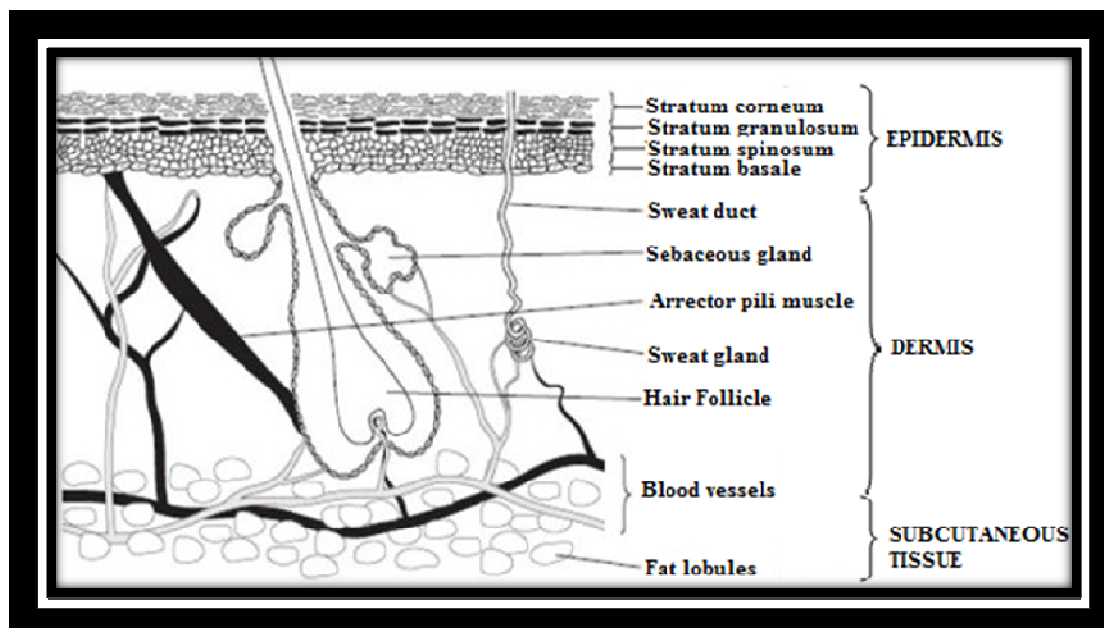


Figure : Cross section of human skin

Epidermis

It is the outermost layer of the skin, which is approximately 150 micrometers thick and is composed of stratified squamous epithelial cells. The epithelial cells are held together mainly by highly convoluted interlocking bridges, which are responsible for the unique integrity of the skin. The epidermis is thickest in the areas of the palms and soles and becomes thinner over the ventral surface of the trunk.

Epidermis show two main parts in the microscopic sections: the stratum corneum and the stratum germinativum.

Stratum corneum forms the outermost layer of the epidermis and consists of many layers of compacted, flattened, dehydrated, keratinized cells in stratified layers. These horny cells have lost their nuclei and are physiologically rather inactive. They are formed and continuously replenished by the slow upward migration of cells produced by the basal cell layer of the stratum germinativum, which is the regenerative layer of the epidermis. Stratum corneum is replenished about every 2 weeks in a mature adult. In normal stratum corneum the cells have a water content of only approximately 20% compared to the normal physiological level of 70% in the physiologically active stratum germinativum. The stratum corneum requires a minimum moisture content of 10% (w/w) to maintain flexibility and softness. It becomes rough and brittle, resulting in so-called dry skin, when its moisture content decreases at a rate faster than can be replenished from the underlying tissues.

The stratum corneum is responsible for the barrier function of the skin. It also behaves as the primary barrier to percutaneous absorption. The thickness of this layer is mainly determined by the extent of stimulation of the skin surface by abrasion and bearing of weight; hence thick palms and soles are developed. In the thicker parts of the skin the transition from the living cells of the germinativum zone to the dead, cornified cells of the stratum corneum is made prominent by three layers, the stratum spinosum (prickly layer), stratum granulosum (granular layer), and stratum lucidum (clear layer). In the process of degeneration, which occurs in this

transition zone, granules of keratohyalin appear in the cells. When these granules have completely changed into keratin, the cells assume a homogeneous appearance to form the stratum lucidum. Like stratum corneum, the stratum granulosum and stratum lucidum are also physiologically important. Removal of these three upper epidermal layers results in water loss and an enhancement of skin permeability.

Dermis

Dermis is made of a network of robust collagen fibers of fairly uniform thickness with regularly spaced cross-striations. This network may; however be an artifact of histological fixation since examination of unfixed dermis by fluorescence microscopy suggests that it is a gel containing oriented tropocollagen (polypeptide) macromolecules. The network or gel structure is responsible for the elastic properties of the skin. Beneath the dermis, the fibrous tissue opens out and merges with the fat containing subcutaneous tissue. On the other hand, the upper portion of the dermis is formed into ridges (or papillae) projecting into the epidermis, which contain blood vessels, lymphatics, and nerve endings. Only the nerve fibers reach into the germinative zone of the epidermis.

Subcutaneous tissue

This layer consists of sheet of fat rich areolar tissue; know as superficial fascia, attaching the dermis to the underlying structure. Large arteries and vein are present only in the superficial region.

Skin Appendages

The skin is interspersed with hair follicle and associated sebaceous gland like regions two types of sweat glands eccrine and apocrine. Collectively these are referred to as skin appendages.

PATHWAYS OF PERCUTANEOUS ABSORPTION⁵

Percutaneous absorption involves passive diffusion of substances through the skin. The pathways of permeation can involve passage through the epidermis itself (transepidermal absorption) or diffusion through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands (transfollicular or shunt pathway absorption).

Transepidermal absorption

It is now generally believed that the transepidermal pathway is principally responsible for diffusion across the skin. The resistance encountered along this pathway arises in the stratum corneum. Permeation by the transepidermal route first involves partitioning into the stratum corneum. Diffusion then takes place across this tissue. The current popular belief is that most substances diffuse across the stratum corneum via the intercellular lipoidal route. This is a tortuous pathway of limited fractional volume and even more limited productive fractional area in the plane of diffusion. However, there appears to be another microscopic path through the stratum corneum for extremely polar compounds and ions. Otherwise, these would not permeate at rates that are measurable considering their o/w distributing tendencies. When a permeating drug exits at the stratum corneum, it enters the wet cell mass of the epidermis and since the epidermis has no direct blood supply, the drug is forced to diffuse across it to reach the vasculature immediately beneath. The viable epidermis is considered as a single field of diffusion in models. It is permeable field that functions as a viscid watery regime to most penetrants. It appears that only ions and polar nonelectrolytes found at the hydrophilic extreme and lipophilic nonelectrolytes at the hydrophobic extreme have any real difficulty in passing

through the viable field. The epidermal cell membranes are tightly joined and there is little to no intercellular space for ions and polar nonelectrolyte molecules to diffusionally squeeze through. Thus, permeation requires frequent crossings of cell membranes, each crossing being a thermodynamically prohibitive event for such water-soluble species. Extremely lipophilic molecules on the other hand, are thermodynamically constrained from dissolving in the watery regime of the cell (cytoplasm). Thus the viable tissue is rate determining when nonpolar compounds are involved.

Passage through the dermal region represents a final hurdle to systemic entry. This is so regardless of whether permeation is transepidermal or by a shunt route. Permeation through the dermis is through the interlocking channels of the ground substance. Diffusion through the dermis is facile and without molecular selectivity since gaps between the collagen fibers are far too wide to filter large molecules. Since the viable epidermis and dermis lack measure physiochemical distinction, they are generally considered as a single field of diffusion, except when penetrants of extreme polarity are involved, as the epidermis offers measurable resistance to such species.

Transfollicular (shunt pathway) absorption

The skin's appendages offer only secondary avenues for permeation. Sebaceous and eccrine glands are the only appendages, which are seriously considered as shunts bypassing the stratum corneum since these are distributed over the entire body. Though eccrine glands are numerous, their orifices are tiny and add up to a miniscule fraction of the body's surface. Moreover, they are either evacuated or so profusely active that molecules cannot diffuse inwardly against the glands output. For these reasons, they are not considered as a serious route for percutaneous absorption. However, the follicular route remains an important avenue for percutaneous absorption since the opening of the follicular pore, where the hair shaft exits the skin, is relatively large and sebum aids in diffusion of penetrants. Partitioning into sebum, followed by diffusion through the sebum to the depths of the epidermis is the envisioned mechanism of permeation by this route. Vasculature sub serving the hair follicle located in the dermis is the likely point of systemic entry.

AN OVERVIEW OF IONTOPHORESIS

I. HISTORICAL BACKGROUND OF IONTOPHORESIS^{3,6}

The method of iontophoresis was described by Varatti in 1747. Galvani and Vota two well known scientists working in the 18th century combined the knowledge that the electricity can move different metal ions and the movement of the ions produce electricity. The method of administering pharmacological agents by iontophoresis became popular at the beginning of 20th century due to the work of Leduc (1900) who introduced the term "ionotherapy" and formulated the laws for this process. He applied Iontophoresis of strychnine and cyanide ions into rabbits and produced titanic seizures and cyanide poisoning. In 1936, Ichihashi observed that iontophoresis of certain applied solutions reduced sweating. He also induced sweating by pilocarpine iontophoresis. Conversely, Gibson and Cooke induced sweating through the Iontophoresis of topically applied pilocarpine. This procedure which was done to measure sweat sodium and chloride concentrations is the basis of the "sweat test," which is used to diagnose cystic fibrosis.

II. PRINCIPLES OF IONTOPHORETIC TREATMENT²

Iontophoresis increases the penetration of electrically charged drugs into surface tissues by the application of an electric current. Electrical energy assists the movement of ions across the stratum corneum according to the basic electrical principle of “like charges repel each other and opposite charges attract”.

The drug is applied under an electrode of the same charge as the drug, and a return electrode opposite in charge to the drug is placed at a neutral site on the body surface. The operator then selects a current below the level of the patient’s pain threshold and allows it to flow for an appropriate length of time. The electrical current significantly increases the penetration of the drug into surface tissues by repulsion of like charges and attraction of opposite charges. The two classically considered prerequisites for iontophoretic treatment is that the drug must be charged (or modified to carry a charge) and that the disease process must be at or near a body surface.

III. THEORETICAL CONSIDERATIONS⁷

Ion Penetration

When salts or drugs are dissolved in aqueous solutions, ionized or electrically charged particles are formed. This process of ion formation is called dissociation or ionization. Ionized drugs do not normally penetrate into surface tissues sufficiently using passive transdermal delivery to achieve a therapeutic level.

The problem of membrane permeation of ionic drugs can be overcome by providing energy source which increases the rate of penetration. Electrical energy, in the form of a small direct current, will assist the movement of ions. According to electrical principles, like charges repel each other and opposite charges attract. Thus, positive drug ions repelled from a positively charged electrode and negative drug ions are repelled from a negatively charged electrode.

Physical and Mathematical Relationships

There are a few relationships that are important in iontophoresis.

Ohm’s Law states:

$$V = IR$$

where V is electromotive force in volts,

I is current in amps and

R is resistance in ohms.

The importance of this relationship is that at constant voltage, any change in resistance results in a change in current level. Very often, the resistance decreases during a procedure; as a result the current, in milliamps, will increase, unless the current device is programmed to deliver a constant current, then the voltage will vary to compensate for changes in resistance.

Coulombs Law states:

$$Q = IT$$

where Q is the quantity of electricity,

I is current in amps and

T is time in minutes.

Thus, “mA·min” is used to describe the “current dosage” used during iontophoresis.

Faraday’s Law states:

$$D = (IT) (IZI F)$$

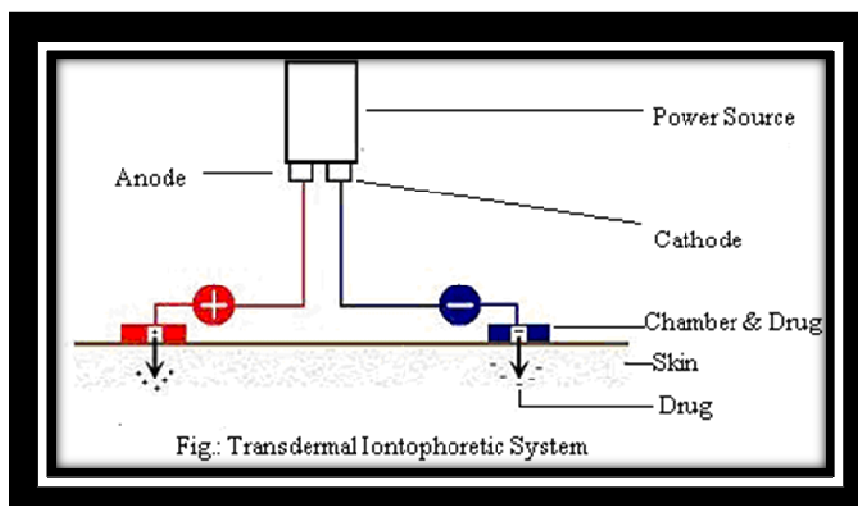
where D is the amount of drug delivered (in gm-equivalents),

I is current in amps,
T is time,
IZI is valance and
F is Faraday's constant.

From this relationship, the more electricity delivered, the more drug delivered. Faraday's law has been used by some to provide information concerning the rate of deposition of the drug at the skin surface.

IV. IONTOPHORESIS MECHANISM AND DEVICES^{3, 8-9}

In iontophoresis, cationic or neutral therapeutic agents are placed under an anode or anionic therapeutic agents under a cathode. When a low voltage and low current density is applied, according to simple electrorepulsion, ions are repelled into and through the skin. Cationic drugs are driven into and through the skin by the anode (active electrode), which also extracts anion from the tissue underneath the skin into the anode. At the cathode (return electrode) anionic buffer ions are driven into the skin and cations from the tissues are extracted into the cathode.



It is also possible to include an additional charged drug in the return electrode to be delivered simultaneously or to use a mixture of drugs in the active electrode to enhance the desired effect or to increase skin permeation, depending on which drugs/molecules are used.

More formally, transdermal iontophoresis should be called electrically assisted transdermal delivery. Iontophoresis enhances transdermal drug delivery by three mechanisms:

- (a) Ion-electric field interaction provides an additional force that drives ions through the skin,
- (b) The flow of electric current increases the permeability of the skin, and
- (c) Electro-osmosis produces bulk motion of solvent that carries ions or neutral species with the solvent stream.

Electroosmotic flow is a flux or bulk fluid induced by a voltage difference across a charged membrane; it is always in the same direction as the flow of counter ions. Since human skin is negatively charged under physiological conditions (i.e. above pH 4), the counter ions are cations and the electroosmotic flow occurs from anode to cathode. Therefore, the cathodic delivery of anions is hindered and the anodic delivery of cations is assisted by electroosmosis.

The improved movement of neutral molecules under iontophoresis is based on electroosmosis. Ions are influenced by all of the above mechanisms so that electroosmosis has a positive

contribution to the transport of cations and a negative contribution to the transport of anions under normal physiological conditions. The impact of electroosmosis on ion transfer increases with the size of the ion. The contribution of electroosmosis can be so significant that the delivery of large anion from the anodic compartment can be more efficient than delivery from cathode; this is called wrong-way iontophoresis. The electrorepulsion effect gives the largest enhancement to the flux of small lipophilic cations. When the concentration of the ionic drug is very high, so that the drug carries most of the current, electroosmotic flow has a very small effect on the drug flux.

Iontophoretic devices may be powered by electricity, batteries or by rechargeable power sources. The machines available in India are electric operated. Battery operated units are Drionic, Phoresor, etc. A Phoreser device consists of a microprocessor controlled battery powered DC current, drug reservoir and electrodes. The batteries are most commonly 9 volt ones. The drug reservoir consists of a gauze/cloth or gel pad to which the solution is applied or the solution is injected through a port into the reservoir electrode combination. Wires are connected between the microprocessor unit and the active and passive electrodes. Iomed iontophoretic drug delivery electrodes are available and are composed of hydrogel material that is hydrated before use to deliver local anesthesia.

V. METHOD OF DELIVERY¹⁰

When applied topically, the current is applied through a moist electrode, the size depending on the skin region to be treated. The drug is administered through an electrode (active) which has the same charge as the drug. This is very important; if the polarity of the electrode is not the same as the ions, then penetration through the skin may not occur. The oppositely charged electrode (return) is placed some distance away at a neutral site, the size and distance of the two electrodes would also affect the transport of ions.

A current intensity below the pain threshold that is comfortably tolerated by the patient is passed for an appropriate length of time (usually below 5mA/cm²). The current intensity should be gradually increased in the beginning and slowly decreased towards the end. The current can be given in any of the different waveforms, square, sinusoidal, triangular etc. The current density is the current intensity per unit cross sectional area. In practice, the density will vary from point to point and the value calculated would be an average value at the electrode surface. What happens here is, the ions transferred through the skin are taken up by the micro-circulation at the epidermo-dermal junction and the current flows back through the return electrode. If any skin irritation occurs at this stage, the current intensity should be lowered.

VI. MERITS OF IONTOPHORETIC DRUG DELIVERY SYSTEM¹¹

- It is a non-invasive technique could serve as a substitute for chemical enhancers.
- It eliminates problems like toxicity, adverse reaction formulation problems associated with presence of chemical enhancers in pharmaceuticals.
- It reduces side effects and avoids the risks of infection, inflammation, and fibrosis associated with continuous injection or infusion since it is non-invasive.
- It permits the use of a drug with a short biological half life since the drug is delivered to the target area without the need to recirculate in the blood. Moreover, the drug is delivered into the bloodstream directly without any delay.
- It may permit lower quantities of drug compared to use in TDDS, this may lead to fewer side effects.

- TDDS of many ionized drug at therapeutic levels was precluded by their slow rate of diffusion under a concentration gradient, but iontophoresis enhanced flux of ionic drugs across skin under electrical potential gradient.
- Iontophoresis prevent variation in the absorption of TDDS.
- It eliminates gastrointestinal incompatibility, erratic absorption, and first pass metabolism.
- Eliminate the chance of over or under dosing by continuous delivery of drug programmed at the required therapeutic rate.
- Provide simplified non-invasive therapeutic regimen, leading to better patient compliance.
- Permit a rapid termination of the effect, if needed, simply by stopping drug input from the iontophoretic delivery system.
- 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, e.g. Thyrotropin releasing hormone, somatotropine, tissue plasminogen activates, interferons, enkaphaline, etc.
- Provide predictable and extended duration of action.
- Reduce frequency of dosage.
- Self-administration is possible.
- A constant current iontophoretic system automatically adjust the magnitude of the electric potential across skin which is directly proportional to rate of drug delivery and therefore, intra and inter-subject variability in drug delivery rate is substantially reduced. Thus, minimize inter and intra-patient variation.
- An iontophoretic system also consists of an electronic control module which would allow for time varying of free-back controlled drug delivery (through variations of current density, pulsed voltage, drug concentration and ionic strength).
- 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.

VII. DEMERITS OF IONTOPHORETIC DRUG DELIVERY SYSTEM¹¹

- 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.
- There is a possibility of burns if the electrodes are improperly used.
- 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, themselves or cosmetically 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 8000-12000 results in a very uncertain rate of delivery.

VIII. FACTORS AFFECTING IONTOPHORESIS TRANSPORT¹²⁻¹⁸

Many factors have been shown to affect the results of iontophoresis. These can be broadly classified into operational and biological factors which are listed below.

A) Operational Factors

- 1) Composition of formulation:
 - a) Concentration of drug solution
 - b) pH of donor solution
 - c) Ionic strength
 - d) Presence of co-ions

- 2) Physicochemical properties of the permeant:

- a) Molecular size
 - b) Charge
 - c) Polarity
 - d) Molecular weight
- 3) Experimental conditions:
 - a) Current density
 - b) Current profile
 - c) Duration of treatment
 - d) Electrode material
 - e) Polarity of electrodes

B) Biological Factors

- 1) Intra and inter subject variability
- 2) Regional blood flow
- 3) Skin pH
- 4) Condition of skin

A) Operational Factors

1) Composition of Formulation

a) Concentration of drug solution

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 flux of a number of drugs e.g., metoprolol, butyrate, diclofenac sodium, dopamine agonist 5-OH DPAT, rotigotine, atenolol HCl and ketorolac. All these drugs showed a proportional increase in flux with an increase in concentration. With drugs like benzoate and LHRH, a modest increase was observed. But this is not the general observation since, a modest increase in concentration increases flux upto a point, after which the flux becomes independent of the donor concentration. This is probably due to the charge saturation of the aqueous conducting pathways of skin also called as boundary layer saturation. Methyl phenidate showed a little change in flux when concentration was increased beyond 0.1M.

b) pH of donor solution

Since iontophoresis is widely used for peptide delivery, pH plays a vital role and it determines the ionization of peptides, which depends upon isoelectric point and respective pK_a of charged amino acid. Moreover skin permeability is also dependent upon pH e.g., AVP (pI- 10.8) showed maximum flux when donor having a wide range of pH (4-8) was used but calcitonin (pI- 6.5) showed optimum flux at pH 4.0 and not at higher pH. 5-OH DPAT showed enhanced flux when pH was increased from 3 to 5 but not at higher pH. In case of leuprolide (LHRH agonist) a two fold increase in flux at pH 7.2 was observed than at pH 4.5.

There was a three fold increase in flux of buprenorphine at pH 4.0 than at pH 5.0. Glibenclamide, when given by pulsed iontophoresis, showed higher flux at pH 8.5 than at pH 7.4 or at pH 8.0. Since pH influences the charge on protein, polarity of electrodes is an important factor to be taken into consideration during drug delivery e.g. anodal delivery of insulin is preferred but below its isoelectric point whereas in case of pilocarpine a moderate pH of 5.98 is required to achieve maximum permeation. Thus, the optimum pH for iontophoretic delivery of a compound is one where it exists predominantly in an ionized form. The effect of pH of aqueous vehicle on rate and extent of iontophoretic delivery of lidocaine was investigated. The rate was found to be maximum when drug was in an ionized form. Therefore, pH is an important factor governing the iontophoretic delivery of drugs. Moreover, it also influences the chemical stability of the drug involved.

c) Ionic strength & Presence of other co-ions

In iontophoresis the main aim is that the drug ion should carry maximum charge across the membrane. It follows that an increase in ionic strength will decrease drug delivery, as extraneous ions compete with the drug ions. 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 itself and can dominate the penetration into the skin thereby causing a decrease in transdermal flux of the drug. Many peptides widely studied for ionic strength showed a higher flux occurring at low electrolyte concentration. Similarly, drugs like ketorolac showed increased flux with decrease in ionic strength. A 50% reduction in benzoate flux occurred when an approximately equimolar amount of NaCl was added to donor compartment. Salicylic acid flux was found to decrease with increase in concentration of HEPES buffer and 5-OH DPAT flux decreased with addition of NaCl. But occasionally an increase in ionic strength leads to an increased flux e.g., iontophoresis facilitated an increased skin permeation of AVP as the ionic strength of donor solution increased.

2) Physicochemical properties of the permeant

a) 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 dodeconate. This suggests that smaller and more hydrophilic ions are transported at a faster rate than larger ions. 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). But due to the use of advanced techniques like iontophoresis, electroporation and phonophoresis, delivery of even large molecule like peptides is possible now.

b) 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 or electrorepletion 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.

c) 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.

3) Experimental Conditions

a) Current strength:

Since current can easily be controlled by the use of electronics, it is a convenient mean to control delivery of drugs to the body. However, a large increase beyond the permissible limits causes irritation and can damage the skin. A linear relationship has been observed between the apparent flux of a number of compounds and the applied current. Methyl phenidate showed a linear relationship between the applied current and its iontophoretic flux. A linear increase in the flux with current has also been found for TRH, verapamil, GRH, diclofenac and ketorolac. In general, 0.5mA/cm² is often stated to be the maximum iontophoretic current which should be used on human beings.

b) 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.

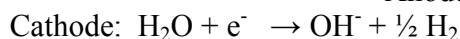
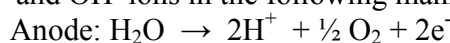
- The current should be sufficiently high to provide a desired drug delivery rate.
- It should not produce harmful effects to the skin.
- There should be a quantitative relationship between the applied current.
- The drug should be electrochemically stable.

c) Current profile:

Application of a continuous current over a long period of time can modulate iontophoresis delivery. Continuous DC current may result in skin polarization, which can reduce the efficiency of iontophoretic delivery in proportion to the length of current application. 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. A two fold increase in the transdermal flux of vasopressin was observed when pulsed current was used *in vivo* in rabbits. Enhanced transport of proteins and peptides has been reported using pulsed DC e.g., insulin. But in many cases like sufentanil, fentanyl and ketorolac a decreased flux was observed when pulsed current was used as compared to constant direct current.

d) Electrode material:

Iontophoretic studies have been conducted using both platinum wire and Ag/AgCl wires. However, platinum electrodes or other inert electrodes like nickel or stainless steel have been found to cause pH drift and gas bubbling due to decomposition of water and thus causing production of H⁺ and OH⁻ ions in the following manner:



Thus, Ag/AgCl electrodes with redox potential lower than that of water which help to maintain electroneutrality at both anode and cathode have been used for this purpose.

Phipps et al. studied the electrode material selection in optimizing delivery of lithium across polyvinyl alcohol (PVA) hydrogel membrane. They showed use of platinum anode in donor caused a pH decrease due to production of hydronium ions as shown above, which are more mobile and no efficient delivery of lithium was observed while the use of Ag/AgCl electrodes in place of caused no pH drift and a significant increase in lithium flux almost double of the above was observed.

B) Biological Factors

a) 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 epidermis has no blood supply.

b) 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. Feldman et al., showed that the passive diffusion of hydrocortisone occurred maximally from the area with numerous hair follicle while lesser in area with thickest corneum.

C) Use of chemical enhancers in Iontophoresis

For a transdermal delivery system to be successful, it should make the drug permeate through the skin to the systemic circulation in quantities sufficient to show the therapeutic effect. In many cases, iontophoresis itself has been able to show an increased permeation of the drug molecule but, in many others, iontophoresis alone has not given desired results which have lead to the use of various chemical enhancers along with iontophoresis to enhance the delivery of drugs especially larger peptide molecules. By both chemical and physical alteration of stratum corneum barrier, the extent of drug absorption can be increased dramatically. Thus, iontophoresis has been used along with chemicals like permeation enhancers to produce a synergistic effect on the permeation of many drugs.

VIII. REVERSE IONTOPHORESIS^{12, 13}

Reverse iontophoresis, a technique in which low electric current is applied to draw intestinal fluid through the skin, is widely applied now a 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 e.g., devices like Gluowatch[®] uses the reverse iontophoretic process to continuously monitor the glucose level in the blood. This system provides a needleless means of monitoring blood glucose levels in diabetic patients and uses an electrical signal that is proportional to the amount of glucose in the extracellular fluid. The GlucoWatch[®] technology requiring calibration with traditional finger-stick glucose measurements is able to provide readings every 20 min for 12 hrs. This is a patient friendly mechanism as regular finger pricks are provided. GlucoWatch[®] is approved for use in children and adults, and is currently indicated only as an adjunctive therapy to conventional blood glucose monitoring.

The technique of reverse iontophoresis provides a feasible method for rapid, linear extraction of phenylalanine and for easy detection (by instrument like biosensors) of monitoring diseases like phenylketonuria. This technique not only provides non-invasive sampling but also provides filtered samples free from large molecules. Although this technique provides for less tedious sampling, for it to be successful, it needs a very sensitive analytical method since the amount extracted is very low.

IX. IONTOPHORESIS (IP) AND ELECTROPORATION (EP) COMBINATION¹²

Iontophoresis has also been used along with other skin penetration enhancing techniques like electroporation, which involves the application of high voltage (>100V) pulses for short duration (μ s-ms) to increase the permeability through the skin. Electroporation is usually applied before iontophoresis, which causes the creation of permeablized skin due to exposure to high voltage pulses. Iontophoresis thus, when applied after electroporation helps in extending the permeablized state of the skin resulting in the rapid onset (which is not possible with iontophoresis alone) and sometimes increased flux. Optimum time for electroporation is desired since if it is not applied for proper time, it may not reduce the lag time sufficiently to produce the desired permeablized skin state which would otherwise facilitate the flux of the drug. The increased transport by electroporation has been found due to creation of electropores as well as local field induced electrophoretic drift. Fang *et al.*, studied the effect of electroporation on the delivery of buprenorphine. They showed that application of 300 V or 500 V pulses increased the buprenorphine flux by several folds over passive transport. Despite the pulsing time of 10 min, the cumulative amount of buprenorphine in the receptor compartment increased constantly till the end of 8 hrs. This suggested that a drug reservoir was created within the skin from where the drug was able to permeate to receptor site after 10 min of application, at a constant rate.

BIOMEDICAL APPLICATION OF IONTOPHORESIS^{10, 21-22}

Iontophoresis has wide applications in Dermatology, Ophthalmology, ENT, Allergic conditions even in Cardiac and Neurological situations, but its greatest advantage is in the transport of protein or peptide drugs which are very difficult to transport transdermally due to their hydrophilicity and large molecular size.

Dermatology

- In hyperhidrosis, especially palmar and plantar – probably by obstructing the sweat ducts. No side effects when compared to anti- cholinergics.
- Copper- iontophoresis for fungal infection and male contraception zinc for ulcers, iodine for reduction of scar tissues, iron/titanium oxide for tattoo removal.
- Histamine in allergy testing.
- In the diagnosis of cystic fibrosis to increase sweating by pilocarpine and confirm diagnosis by the concentration of sodium and chloride in the sweat.
- In scleroderma, for iontophoretic delivery of hyaluronidase.

Ophthalmology

Iontophoretic induction of various drugs like atropine, scopolamine, sulfadiazine, fluorescein, gentamycin etc.

ENT

For providing anaesthesia of the external ear canal and middle ear and in maxillo facial prosthetics surgeries.

Dentistry

To prevent dentin hypersensitivity and for providing local anaesthetic for multiple tooth extraction.

Neurophysiological and Neuropharmacological studies

As a research tool, micro-iontophoresis can be used to study neuro muscular junction, peripheral and central nervous system and smooth muscle preparations.

Delivery of drugs

Antihypertensives, anti-diabetics, anti-rheumatoids, hormones, vasodilators: metoprolol, propranolol, insulin, methylcholine, bleomycin, steroids have all been introduced iontophoretically.

Musculo skeletal disorders

Magnesium sulphate for bursitis, Calcium for myopathy, Silver for osteomyelitis, local anaesthetics and steroids into elbow, shoulder and knee joints.

Cardiology:

Iontophoretic transmucosal drug delivery of anti-arrhythmic drugs which would avoid high systemic toxic levels is being done in animals.

For relief of pain

- Iontophoretic histamine delivery as counter-irritant
- For post-operative pain relief
- For iontophoretic delivery of local anaesthetics for referred pain
- Anti-inflammatory drug delivery

CONCLUSION

Iontophoresis, is one of the most promising methods to enhance delivery of drugs with poor permeation profile through the skin. This is especially true for high molecular weight compounds e.g. proteins, peptides, and oligonucleotides, which can only be administered through parenteral route having many obvious disadvantages. 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 largely incapable of transdermal penetration due to the skin's lipophilic nature. Iontophoresis is gaining wide popularity as it provides a non-invasive and convenient means of systemic administration of drugs with poor bioavailability profile, short half life and with multiple dosing schedules. Iontophoresis, in comparison to oral route, definitely provides benefits of improved efficacy and/or reduction in adverse effects. For topical delivery of drugs like lidocaine (Lidosite[®]), iontophoresis provides an obvious advantage of getting quicker onset of action and minimization of side effects due to avoidance of large oral doses to get local action on the skin. Many characteristics of

iontophoresis must be controlled to achieve successful drug delivery. These include mainly the factors which can affect the iontophoretic delivery of drugs like the operational factors and biological factors. The charge, concentration, and drug combinations must be compatible with the entire process of iontophoresis. Besides this, preservatives, buffers, osmotic agents, stability and conductivity of the vehicle, are also important for the process of iontophoresis to be successful. Many studies involving the use of combination approaches like use of various chemical enhancers along with iontophoresis have lead to significant improvement in absorption of insulin and many other drugs, which could not be delivered using iontophoresis alone. Use of pulsed form of DC has also been used and has shown to produce significant and rapid delivery of drugs. Other types of iontophoretic techniques like reverse iontophoresis, have opened a new era in the diagnostic field, as it provides a non-invasive and less tedious sampling of body fluids. The major advantages of iontophoretic delivery system which make its future use hopeful on large scale are the accurate control over drug input kinetics and optimization of drug input rates. In the future, this system might be used to deliver therapeutic proteins or vaccines transdermally. Thus, iontophoresis may prove to be an important alternative method of drug delivery in the near future.

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