Iontophoresis: fundamentals, developments and application

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Abstract

The skin is an excellent barrier to the transport of charged compounds and large molecules. Many substances of present and potential therapeutic utility carry charge at physiological pH, have high molecular weights and/or are hydrophilic and, consequently, do not transport well across the skin. Pathways for the transport of small ions do appear to exist through the skin and flow along these pathways can be substantially enhanced by iontophoresis.

Key words: iontophoresis, transport, patches, application

Introduction

Drug delivery technology allows the right dose of an active pharmaceutical ingredient to be delivered at the right time, and most importantly, to the right site. It is playing an increasingly important role in lowering the cost of health care. New formulations are no longer simply line extensions intended to prolong a drug's lifecycle, but strategic weapons that have real economic value in disease management. For major drug companies, the addition of an improved drug delivery formulation, either clinically or through improved patient compliance, can often mean the difference between being on or off a formulary.

Transdermal drug delivery systems (TDDs) facilitate the passage of therapeutic quantities of drug substances through the skin and into the general circulation for their systemic effects. Evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and/or its metabolites in the urine, and through the clinical response of the patient to the administered drug therapy. With transdermal drug delivery, the blood concentration needed to achieve therapeutic efficacy may be determined by comparative analysis of patient response to drug blood levels. For transdermal drug delivery, it is considered ideal if the drug penetrates through the skin to the underlying blood supply without drug build up in the dermal layers.

Multiple methods exist for transdermal drug delivery. There is great interest between pharmaceutical scientists to develop physical methods and chemical permeation enhancers that can increase the percutaneous absorption of therapeutic agents.

Definition

Iontophoresis is a process or a technique which involves the transport of ionic (charged) molecules into a tissue by the passage of a direct electric current through an electrolyte solution containing the ionic molecules to be delivered, using an appropriate electrode polarity. It involves the transfer of ions into the body by an electromotive force. Ions with positive charge are driven into the skin at the anode and those with negative charge at the cathode.

This technique is used to enhance the transdermal transport of drugs by applying a small current through a reservoir that contains ionized species of drug. Positive or negative electrodes are placed between the drug reservoir and the skin. Positive ions are introduced in the skin from positive electrode, and negative ions from a negative electrode.

Principles of ionic transport in an electric field

The transport of ions under the influence of a uniform electric field was first studied by Planck. The Nernst-Planck equation, a fundamental equation widely used to describe the membrane transport of ions (1,2) is written as:

$$J_i = -D_i \frac{dC_i}{dx} + \frac{D_i z_i e_i E C_i}{kT}$$

where J_i is the flux of ions across the membrane, D_i is the diffusion coefficient of the ion i (in the x direction), C_i is the concentration of ions with valence z_i and electron charge e_i, E the electric field. The term kT is the thermal energy of the system where k is the Boltzmann constant and T is the absolute temperature.

A better appreciation of the meaning of this equation may be achieved by considering the case of a nonelectrolyte in which case the charge, z_e, equals zero. In this case, Nernst-Planck equation becomes:

$$J_i = -D_i \frac{dC_i}{dx}$$

which is Fick's first law of diffusion. On the other hand, for an ion with a uniform concentration throughout the system (d*C*/dx=0), the Nernst-Planck equation becomes:

$$J_i = \frac{D_i z_i e_i E C_i}{kT}$$

The Nernst-Planck equation may be thus interpreted as implying that when a concentration gradient and and electric field both exist, the ionic flux is a linear sum of the fluxes that would arise from each effect alone. Verification of the validity of the Nernst-Planck equation can be achieved by using thermodynamic expressions for chemical potential, since the driving force on the i^{th} species is the negative gradient of its chemical potential.

Electrical properties of the skin

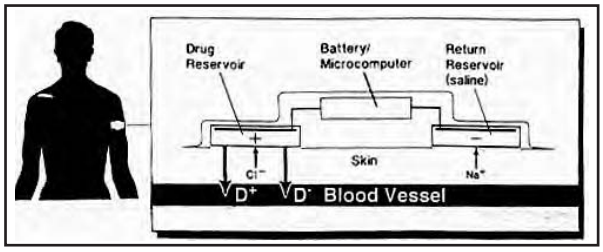
Stratum corneum is composed of layers of horny cells which are a good insulator, and forms the principal barrier of the body to electrical conductivity. The relative conductivity of various tissues is known to be about equal to their water content, and the water content in the stratum corneum is about 20%, much lower than the normal physiological level of 70%. As the stratum corneum forms the high electric layer, it is very important element for skin impedance. To understand the concept of impedance, the term called capacitance must be introduced: a pair of plates are arranged at parallel position and separated by a very small distance and connected to a battery which allows electrons to distribute over the lower plate. The electrons on the lower plate then induce a positive charge on the upper plate, so that more electrons can now flow into the lower plate from the battery. This arrangement of parallel plates acts as a capacitor (or condenser) and this property is called capacitance. Thus, the capacitance of a capacitor is its ability to store an electric charge, flowing into it in the form of current. Biological tissues such as skin tissue also have a capacitance because of their ability to store electrons, and are thus electrically capacitors.

Iontophoretic patches

An iontophoretic patch (Figure 1) consists of three main components (3):

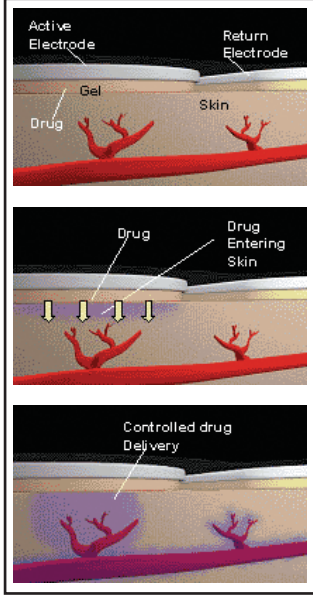
1. An aqueous drug reservoir that is usually biocompatible gel or adsorbent-pad material. Positively charged ions are placed at the positive pole, while negatively charged ions are placed at the negative pole.
2. A return reservoir that completes the circuit. Typically, thic circuit is a saline formulation.
3. An electronic controller that is programmable to give a complicate dosing feature.

Figure 1. Simplified representation of the components of an iontophoretic patch.



Transdermal drug delivery platform employing an adhesive patch containing medication and a small electronic dose controller. The patch consists of two pre-loaded reservoirs, a drug reservoir that contains the drug to be delivered and a return reservoir with saline to complete the circuit. The controller contains a battery and a pre-programmed microcomputer to control the electrical charge. The two components connect through an interface (Figure 2).

Figure 2. Iontophoretic system-way of drug delivery



An adhesive patch contains thin electrode and the drug-containing gel in contact with the skin;

The battery powered micro-controller activates the electrode with a mild current repelling the drug into the skin;

Depending on the dose and energy the drug can act either locally or can be carried into the bloodstream;

Factors affecting iontophoretic transport

Many factors have been shown to affect the results of iontophoresis. These include the physiochemical properties of the compound (molecular size, charge, concentra-

tion), drug formulation (type of vehicle, buffer, pH, viscosity, presence of other ions), equipment used (available current range, constant vs. pulsed current, type of electrode), biological variations (skin site, regional blood flow, age, sex), skin temperature and duration of iontophoresis.

A) Influence of pH

The pH is of importance for the iontophoretic delivery of drugs. The optimum is a compound that exists predominantly in an ionised form. When the pH decreases, the concentration of hydrogen ions increases, and a vascular reaction (vasodilatation) is initiated because of C-fibre activation. Thus, it is important to keep the pH as close as possible to 7, at least when working with vasodilators. At pH 5.5 and below, there is an increasing risk for vascular reactions due to the high concentration of hydrogen ions rather than the compound used. Since hydronium ions are small, they penetrate the skin more easily than larger drug ions.

B) Current strength

There is a linear relationship between the observed flux of a number of compounds and the applied current. With the electrode area of 1 cm^2, the current is limited to 1 mA due to patient comfort considerations. This current should not be applied for more than three minutes because of local skin irritation and burns. With increasing current, the risk of non-specific vascular reactions (vasodilatations) increases. At a current of 0.4 to 0.5 mA/cm^2, such a vascular reaction is initiated after a few seconds of iontophoresis with deionised or tap water.

C) Ionic competition

In a solution of sodium chloride, there is an equal quantity of negative (Cl^-) and positive (Na^+) ions. Migration of a sodium ion requires that an ion of the opposite charge is in close vicinity. The latter ion of opposite charge is referred to as a counter-ion. An ion of equal charge but of a different type is referred to as a co-ion.

When using iontophoresis, it is important to know that pH adjustment is performed by adding buffering agents. The use of buffering agents adds co-ions which are usually smaller and more mobile than the ion to be delivered. This results in a reduction of the number of drug ions to be delivered through the tissue barrier by the applied current. This means that when a positively charged drug is diluted in saline, the sodium ions will compete with the amount of drug ions to be delivered. Ideally, the use of a buffer system should be avoided in iontophoresis, but if this is not possible, alternative buffers consisting of ions with low mobility or conductivity are preferred.

D) Drug concentration

Depending on the drug used, the steady-state flux (ion movement) has been shown to increase with increasing concentration of the solute in the donor compartment, i.e. in the delivery electrode. A limiting factor to be considered is the strength of the current used. At higher drug concentrations, the transport may become independent of concentration, probably because of the saturation of the boundary layer relative to the donor bulk solution (4) .

E) Molecular size

It has been shown that the permeability coefficients in positively charged, negatively charged and uncharged solutes across excised human skin are a function of molecular size. When the molecular size increases, the permeability coefficient decreases. However, there are certain solutes with a relatively high molecular size (e.g. insulin, vasopressin and several growth hormones), which have also been shown to penetrate the skin barrier into the systemic circulation.

F) Convective or electro-osmotic transport

When performing iontophoresis with a specific current, the flow of ions across the membrane induces a flow of solvent called electro-osmosis. Compared to the ion transport, the electro-osmotic contribution is small. The penetration of uncharged substances (e.g. bovine serum albumin) has been shown to be facilitated by the volume flow effect induced by an applied potential difference across the membrane. Iontophoresis has also been observed to enhance the penetration of a number of dipolar ions (zwitterionic substances, such as phenylalanine) . Most of these substances have been shown to be delivered in significantly higher amounts by anodic delivery than by cathodic delivery. In general, iontophoresis is more effective for charged compounds, especially monovalent ions.

G) Current - continuous vs. pulsed mode

Application of a continuous current over a long period of time can modulate iontophoretic delivery. Continuous DC current may result in skin polarisation, which can reduce the efficiency of iontophoretic delivery in proportion to the length of current application. This polarisation can be overcome by using pulsed DC, a direct current that is delivered periodically. During the "off time", the skin becomes depolarised and returns to its initial unpolarised status. The enhanced skin depolarisation using pulsed DC can, however, decrease the efficiency of pulsed transport if the frequency is too high (5).

H) Physiological factors

Iontophoresis reduces intra- and inter-subject variability in the delivery rate. This is an inherent disadvantage with the passive absorption technique. Experiments *in vivo* and *in vitro* 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. The status of the vascular bed is also important; for instance, a pre-constricted vascular bed decreases the drug flux through the skin while a dilated vascular bed increases the yield of the drug through the skin.

Optimising iontophoretic transport

1. Iontophoretic transport can be regulated by varying the applied current density and area of application. A current density that is too high may be unpleasant for the patient. If possible, avoid using current settings that result in more than 500 mA/cm^2. At high current densities, there is a significant risk for unspecific electrically mediated vasodilatation that is not drug related.

2. The pH of the formulation should be optimised to ensure maximum ionisation of the compound. To prevent pH drifts during the iontophoresis, the choice of electrodes is of importance. With a correct electrode material, decreased solubility and precipitation of the compound are avoided.

3. Before iontophoresis is carried out, carefully clean the skin area to be used with deionised water or preferably 70 per cent alcohol. Cleaning will decrease the current needed and minimise the risk for local spots of high current density, which could result in C-fibre activation, vasodilatation and local micro-burns.

Advantages and disadvantages of iontophoresis

Advantages of iontophoresis

There are several advantages to iontophoretic drug delivery methods:

- The risk of infection is reduced because it is non-invasive there is no mechanical penetration or disruption of the skin to cause pain.
- Drug solutions are delivered directly to the treatment site without the disadvantages of injections or orally administered drugs, avoiding first pass metabolism.
- It eliminates multiple dosing per day.
- It provides a relatively pain-free option for patients who are reluctant or unable to receive injections. For example, with appropriate controls, iontophoresis can be an extremely attractive method for delivering drugs such as analgesics for the treatment of acute pain - the drug can be rapidly delivered for absorption and can, with appropriate controlling technology, be self-administered on demand by the patient
- It minimizes the potential for further tissue trauma that can occur with increased pressure from a fluid bolus injection.

Disadvantages of iontophoresis

Major side-effects are very rare when using iontophoresis as a diagnostic tool. However, minor reactions such as itching, erythema and general irritation of the iontophoretic skin surface are common. There is an increased risk of minor reactions if the exposure time and/or current are increased, and with some drugs like histamine, capsaicin and acetylcholine. Some drugs induce long-lasting skin pigmentation after iontophoretic application, where the intensity of skin discoloration is proportional to the exposure time.

The current density across the pores in the skin may be higher than the current per unit area applied, depending on the density of pores in a given area. These spots of high current density increase the possibility of current-induced skin damage.

It was shown (6) that the skin resistance was always less than the initial value when a current of 0.16 mA was applied for 10 minutes. This may result in a permanent skin damage. This phenomenon may explain the sudden vascular response with iontophoresis of deionised water, which seems not to be related to the dose. Under the microscope, small spots of skin damage within the pore area could be recognised. The vasodilatation initiated in this way may be caused by activation of nociceptive fibres terminating in the epidermis, which initiate an axonreflex mediated vascular response.
Although widely available, iontophoresis, to date, has been minimally employed. Technical issues have had to be overcome, in order to take full advantage of the approach. For example, the skin is relatively impermeable, and drug ions do not cross easily into the underlying tissue. Consequently, only smaller molecular weight drugs (generally under 10,000 Daltons) that are water-soluble are good candidates for delivery. Additionally, some patients, with certain formulations, experience redness, burning, and/or itching at the administration site.
Perhaps a key disadvantage to the technology has been the lack of adequate delivery control and a low-cost,

long-lasting power source - optimizing the device relies on electrical current to deliver the drugs over a prescribed period of time in a carefully controlled manner

Contraindications for iontophoresis

Contraindications for iontophoresis are important in patients with higher susceptibility to applied currents. Such patients include those carrying electrically-sensitive implanted devices such as cardiac pacemakers, those who are hypersensitive to the drug to be applied, or those with broken or damaged skin surfaces.

Application of iontophoresis

Iontophoresis can be considered as an interesting alternative to parenteral route, particularly in the case of peptide drugs (e.g. insulin, calcitonin), macromolecular substances in ionized state at physiological pH values, that are poor absorbed and extensively degraded by proteolytic enzymes in the gastro-intestinal tract, showing extremely low bioavailability when administered orally.

Iontophoresis has been extensively investigated for local absorption of topically applied drugs (diagnosis of cystic fibrosis with pilocarpine, local anaesthetic with lidocaine, in the therapy of osteoarthritis, rheumatism, tendonitis -glucocorticoids, non-steroid analgetics, in the therapy of surface tissue diseases Herpes Simplex infections and psoriasis-acyclovir and khellin).

Conclusions

Iontophoresis offers the benefits of being painless and non-invasive. In addition, there is no danger of infection or damage due to needle insertion or to impact from a bolus of fluid. The local concentration of the drug is high, while the systemic concentration is minimal. Only minute amounts of the drug reach the systemic circulation, greatly reducing side effects. Drug dosage is accurately controlled by controlling the quantity of electrical current used to transfer the drug. Exposure to mild electrical current provides added therapeutic effects. Contraindications with this modality pertain to sensitivity to the drug rather than to the modality itself. The manufacturer suggests avoiding electrode placement so that the current pathway crosses the heart or the brain. Also the area of the eye should be avoided. Abraded skin or new scar tissue should be avoided as these areas are sensitive to electrical current, making the treatment uncomfortable. The equipment available today is efficient and miniaturized. The possibility of shock or burns, a problem with iontophoresis in the past, are now eliminated by advanced electrode design and modulated current. Iontophoresis has the potential to provide substantial benefits when this mode of therapy is applied in the appropriate manner (7). There is little doubt that many substances can be introduced into the body by this method. Iontophoresis offers a means of introducing medications through the surface of the skin in a safe, easy and painless manner. As with many new modes of therapy, however, there is need for more studies that document the use and effects of iontophoresis in various clinical situations.

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