Transdermal Iontophoresis

Transdermal Delivery

The skin is the largest organ in the body and, with its large surface area, represents an attractive route for drug administration. Several transdermal systems have been developed and marketed for the relief of pain, contraception, hormone replacement, motion sickness, hypertension and angina. Transdermal drug delivery systems provide distinct benefits due to elimination of hepatic first-pass effects, reduction in systemic side effects by decrease in initial dose size and increased patient compliance. However, development of formulations and systems for transdermal delivery has been hindered by poor tissue permeability – predominantly in the outermost layer of the skin – known as the stratum corneum (SC).

The SC consists of a well-organised layer of dead corneocytes intercalated with lipids, which present a significant barrier to the diffusion of agents into the body. In order to overcome this barrier and enhance permeation, a number of chemical and physical enhancement techniques have been developed either alone or in combination. Though chemical enhancers increase delivery of agents by perturbing the SC barrier through interaction with proteins or by fluidisation of the SC lipids, their extensive use is limited by their potential skin irritation.1–3 Similarly, various physical enhancement techniques such as iontophoresis,4 phonophoresis,5 electroporation6 and microneedles7 have also been examined. Transdermal iontophoresis involves the use of a constant/pulsed current to develop an electric potential gradient that forces the ionised drug into the skin. Various transdermal iontophoretic devices have been successfully developed and marketed, the latest being the LidoSite™ patch (Vyteris, Inc.)8 Transdermal iontophoresis has not only enabled the successful delivery of small molecules such as fentanyl hydrochloride (E-TRANS® patch, ALZA Corp.) for pain management,9 but also delivery of peptides such as insulin, nafarelin and luteinising hormone-releasing hormone (LHRH).11,12

Basic Principles of Transdermal Iontophoresis

This technique is based on the principle that application of electric current provides external energy to drug ions for passage across the skin, thereby increasing drug permeability through the membrane.10 A typical iontophoretic drug delivery system consists of an anode, a cathode and two reservoirs, one comprising drug ions and the other containing biocompatible salt such as sodium chloride.11 For delivering positively charged ions, two iontophoretic approaches have been developed, namely anodal and cathodal iontophoresis. In anodal iontophoresis, cationic drug ions are placed under the anode at the desired site of application and the cathode (receiving electrode) is placed at a different site on the skin, whereas in cathodal iontophoresis the electrode orientation is reversed.12 The movement of ions in iontophoresis follows the basic rule of electricity, i.e. like charges repel each other. In anodal iontophoresis, on application of current, all drug cations (and other positively charged ions) placed at the anode move away from the anode (positive electrode) and pass into the skin, and at the same time anions from the body are repelled from the cathode and migrate into anodal reservoir (see Figure 1). The efficiency of transdermal iontophoresis can be calculated from the slope of a plot of the iontophoretic drug delivery versus current applied.13 The amount of permeant delivered across the skin is directly proportional to the quantity of charge passed through the membrane, which in turn depends on the amount and duration of the applied current and the skin surface area in contact with the electrode compartment.13

Theory of Drug Transport by Iontophoresis

Iontophoretic drug delivery occurs by a combination of:

• concentration gradient (diffusive/passive transport component) and electrochemical potential gradient developed across the skin;

• increased skin permeability under applied electric current (electromigration/electrorepulsion); and

• a current-induced water transport effect (electro-osmosis/convective transport/iontohydrokinetics).12,14

It should be noted that iontophoretic drug transport is mainly through electrorepulsion and electro-osmosis; the passive component plays an insignificant role. Electrorepulsion refers to the drug transport across skin due to either the repulsion of cations into the skin from the anode (anodal iontophoresis) or the migration of anions into the skin from the cathode (cathodal iontophoresis). On the other hand, electro-osmosis is a phenomenon that occurs as a result of a net negative charge on the skin at physiological pH (7.4) that subsequently leads to its cation permeability. This results in induced solvent flow that facilitates cation transport in anode-to-cathode direction, with inhibition of anion transport enabling enhanced transdermal delivery of neutral and polar solutes across the skin when an electric field is applied.16,19 It has been reported in the literature that the iontophoretic delivery of small, highly mobile ions such as sodium ions, which are efficient charge carriers, is dominated by electrorepulsion. However, electro-osmosis is the primary transport mechanism of larger and bulkier species, such as cationic peptides of molecular weights in the order of 1,000 Daltons or more.10

Advantages and Limitations of Iontophoresis

Iontophoresis, like passive transdermal drug delivery, bypasses the first-pass hepatic metabolism and gastrointestinal degradation. It maintains controlled plasma levels of drugs, even those with short biological half-lives, and also offers the benefit of delivering charged and high-molecular-weight compounds, unlike passive transdermal delivery, which
is limited to small, non-polar and lipophilic solutes. Iontophoresis also provides increased patient compliance due to less frequent dosing, ease of terminating drug delivery at any stage of therapy and the capability of tailoring drug therapy at pre-programmed rates according to individual needs.\textsuperscript{[12,17]} The inter- and intra-subject variability is also reduced as the rate of drug delivery is directly proportional to the applied current.

Though it offers numerous advantages, application of iontophoresis is limited to drugs that can be formulated in the ionic form.\textsuperscript{[18]} Also, during iontophoretic transport across the skin, the drug encounters potential of hydrogen (pH) differences ranging from 4 to 7.3, leading to the possibility of the drug molecule becoming uncharged and losing the major effect of electric field. For peptides and proteins that undergo charge reversal in their passage through skin, this phenomenon may lead to their delivery out of the skin instead of into the skin. In addition, the delivery efficiency is reduced by competition from interfering ions (of the same charge as the drug ions). Lastly, increasing the current intensity or applications for long periods can lead to pain, burning sensations, skin irritation, erythema, blister formation and skin necrosis,\textsuperscript{[16]} and iontophoresis is not recommended for underarm or facial/head hyperhidrosis.\textsuperscript{[17]} Also, the high-energy requirement in iontophoresis for sustained therapeutic delivery influences the size and cost of the dosage form making its use less economical.\textsuperscript{[18]}

### Pathways of Skin Transport by Iontophoresis

Despite the use of an electric current, iontophoresis primarily enhances transport via the already existing pathways in the skin, mainly the transappendageal (hair follicles and sweat glands) and the paracellular route.\textsuperscript{[19]} This was demonstrated by Cullander and Guy,\textsuperscript{[20]} who used vibrating probe electrodes to identify site-specific ionic flows occurring in hairless mouse skin. The iontophoretic pathways were found to be appendageal and certain appendages, mainly the small hairs, appeared to carry the most current. Others have used visualisation techniques, such as confocal laser scanning microscopy (CSLM),\textsuperscript{[21]} to view the pathway of iontophoretic transport post-iontophoresis and passive treatment of hairless mouse skin with fluorescently labelled poly-L-lysines (FITC-PLLs).

The enhanced penetration due to iontophoresis was observed mainly along the hair follicles in the skin especially in the deeper layers (20–40µm below the skin surface). Involvement of non-appendageal pathways for iontophoretic transport has also been suggested,\textsuperscript{[20]} which includes the creation of artificial shunts due to disruption of the stratum corneum structure,\textsuperscript{[12]} a temporary pore formation due to ‘flip-flop’ movement in the polypeptide helices in the stratum corneum\textsuperscript{[22]} or pathways of least resistance created by damaged skin areas. In addition, other factors such as the source and structure of skin and the density of hair follicles will contribute to the determination of the transport pathways.\textsuperscript{[23]}

### Factors Influencing Iontophoretic Transport

Several factors play a role in influencing iontophoretic transport, the most important being the physicochemical properties of the active agent (concentration, molecular charge, size), formulation factors (pH, ion competition, type of buffer), the iontophoretic system (amount and time of applied current, electrodes) and the membrane used.\textsuperscript{[12,17]} One of the most critical factors is pH, as this influences the amount of drug available in its ionised form. Iontophoretic transport of lidocaine was found to be highest at pH 8.5 where the molecule exists mainly in the ionised form,\textsuperscript{[24]} and similar trends have been demonstrated with other solutes;\textsuperscript{[25]} pH is also very significant for peptides as it can control the amount of charge on the molecules based on their isoelectric point. In addition, the pH changes that occur at the electrodes concurrent with the iontophoresis process can affect drug transport. Electromigration of the ions also increases with their rising concentration in solution, and is negatively influenced by the presence of other ions of similar charge (often a result of added buffers) or opposite charge. Influence of the molecular size on iontophoretic transport has been described by a linear relationship between the logarithm of the iontophoretic permeability coefficient and the molar volume. However, solutes of high-molar volumes, such as insulin and other hormones, have also shown significant iontophoretic transport.

Besides the properties of the molecule and the formulation, various aspects of the iontophoretic system affect the transport across membranes. The iontophoretic flux has been shown to be proportional to the current intensity, and this phenomenon has been reported in vitro for thyrotropin-releasing hormone (TRH),\textsuperscript{[26]} sodium and lithium\textsuperscript{[11]} and verapamil,\textsuperscript{[27]} and also in vivo for pyridostigmine.\textsuperscript{[13]} However, the increasing flux may reach a plateau, implying presence of saturation.\textsuperscript{[28]} Moreover, the amount of current is also restricted by the skin irritation and discomfort it may cause.

Though most studies have used continuous direct current, the choice of pulsed current has led to equally effective or better transport efficiency while giving the skin time to recover in between the pulses, at the same time preventing accumulation of charges.\textsuperscript{[29]} The type of electrodes used also influences the transport rate, hence they should be of good conductive material and should contour well on the skin surface. Silver/silver chloride (Ag/AgCl) electrodes are most commonly used because they are reversible and resist changes in pH. Other electrodes used are platinum or zinc/zinc chloride wires.\textsuperscript{[30]} Last, physiological factors such as age, race, thickness and perme selectivity of the skin, injuries and blood flow impart some variations in iontophoretic transport.

### Applications of Transdermal Iontophoresis

Transdermal iontophoretic systems have the potential to produce reproducible enhancement of transdermal delivery of molecules at

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**Figure 1: Iontophoresis Using a Silver/Silver Chloride Electrode System**

Electromigration transports the cations, including the drug molecule, from the anodal compartment into the skin, while the endogenous anions, primarily Cl\textsuperscript{\text{−}}, move into the anodal compartment.

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levels that are therapeutically significant. They also enable the programming or control of the drug kinetics through the device. These properties make the system suitable for the delivery of a wide range of molecules, including several macromolecules that demonstrate limited passive permeation.

Enhancement of transdermal delivery by iontophoresis has been demonstrated for several small molecules such as apomorphine, sumatriptan, sumatriptan sulphate, and buspirone hydrochloride. Combination of iontophoresis of small molecules with other enhancement strategies has also successfully led to significant permeation enhancement through the skin. Tiwari and Udupa found that the combination of chemical and physical enhancer pre-treatment (ultrasound, iontophoresis and pre-treatment with 5% D-limonene in ethanol) gave rise to a flux (136.11±9.10µg/cm²/h) that was significantly different from iontophoresis alone (flux: 62.80±6.78µg/cm²/h) as well as from treatment with the chemical enhancers and ultrasound alone.

Iontophoretic drug delivery systems have also generated interest in enhancing the delivery of macromolecules such as peptides, which are often polar, carry a charge and cannot be administered via the oral route due to poor absorption and stability. Insulin has been a popular candidate for iontophoretic delivery and has been investigated extensively, mostly in combination with chemical enhancer pre-treatment or other enhancement techniques. Most of these studies have led to significant flux enhancement of insulin and in many cases delivery of the therapeutic dose. Recently, Akimoto et al. reported similar results and found that the iontophotically enhanced skin permeation of insulin increased linearly with the density of pulsed direct current applied. Several other macromolecules such as LH/FSH and nafarelin have also been investigated for iontophoretic transport. The effectiveness of iontophoresis of small molecules with other enhancement techniques such as electroporation or ultrasound or with chemical enhancers has led to the observation of significantly higher flux levels compared with passive transdermal delivery. However, the resulting irritation caused to the skin due to combined strategies may be a cause for concern. Also, electrically assisted delivery systems provide the advantage of controlled drug delivery with customised drug input rates, and an option of ceasing drug transport when desired. In addition, iontophoresis is also finding value in drug delivery via other drug administration routes such as transconveal and trans-scleral routes, and also through bone for delivery of antibiotics to prevent infection during allograft implantation.

**Conclusions**

Iontophoretic drug delivery systems form a major group of the relatively few physically enhanced transdermal delivery systems that have been successfully developed and commercialised. The electrically driven penetration enhancement provided by this method has succeeded in overcoming the formidable barrier presented by the SC, and has shown to be a promising technique for various agents, including macromolecules. Combination strategies with other physical enhancement techniques such as electroporation or ultrasound or with chemical enhancers have led to the observation of significantly higher flux levels compared with passive transdermal delivery. However, the resulting irritation caused to the skin due to combined strategies may be a cause for concern. Also, electrically assisted delivery systems provide the advantage of controlled drug delivery with customised drug input rates, and an option of ceasing drug transport when desired. In addition, iontophoresis is also finding value in drug delivery via other drug administration routes such as transconveal and trans-scleral routes, and also through bone for delivery of antibiotics to prevent infection during allograft implantation.
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