

Iontophoretic Topical and Transdermal Drug Delivery

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Introduction

Transdermal delivery has been one of the more successful drug delivery approaches. The 'Patch' is now a household word. This is partly due to the heavy advertisement of nicotine patches, now readily available over the counter, as an aid to smoking cessation. Several other drugs are on the market in a patch form, including clonidine, estradiol, fentanyl, nitroglycerin, oxybutynin, scopolamine and testosterone. Multiple brands are on the market for some of these drugs, such as nitroglycerin, and generic patches for other drugs, e.g. fentanyl, have now started to appear. Topical patches for lidocaine and estrogen/progestin combination for birth control are also available.

All these drugs are small lipophilic molecules. The skin is normally not permeable to water-soluble molecules and permeability of larger water-soluble molecules, such as peptides and proteins, is further limited. In recent years, there has been increasing interest in enhancement technologies that can expand the scope of transdermal delivery to hydrophilic molecules and macromolecules. These technologies include use of electric energy (iontophoresis and electroporation) or acoustic energy (phonophoresis or sonophoresis) or physical temporary disruption of the skin barrier by techniques such as microporation. This report will discuss the potential applications of iontophoresis for topical and transdermal drug delivery.

Iontophoresis: What is it?

Iontophoresis uses a low-level electric current to drive ionised drug molecules into or through the skin (Banga, 1998). Typically, the current may be about 0.2 mA/sq cm and is imperceptible at this level. By using an electrode of the same polarity as the charge on the drug, the drug is driven into the skin by electrostatic repulsion (*Figure 1*). Since the drug is delivered in proportion to the current, it is possible to program the delivery to tailor it to the needs of the individual patient. Iontophoresis is a safe procedure though patients may experience some tingling and/or itching as the current is ramped up and it may induce a transient and reversible mild skin irritation (Li *et al.*, 2005).

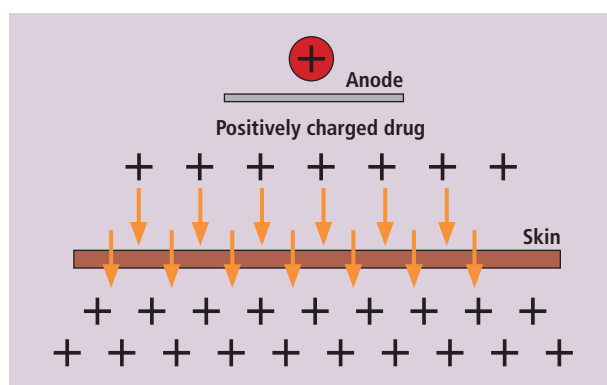


Figure 1 – Schematic for the iontophoretic delivery of a positively-charged drug across skin under anode.

Iontophoresis is most suited for water-soluble drugs of an ionic nature though water-soluble neutral drugs can also be delivered. This is because electro-osmotic flow of water takes place during iontophoresis, which can carry drugs dissolved in water across the skin, even if they are not charged. The technique is particularly promising for delivery of peptides and small proteins (MW < 10 kDa) since these drugs cannot be delivered orally and have short half-lives. There is, therefore, an urgent need for a non-invasive alternative to frequent injections. Polypeptides which have a high isoelectric point are ideal candidates as they retain their charge during transport into and across the skin. Peptides with isoelectric points inside the pH range of skin (e.g. insulin) have significant problems to overcome (Banga, 1998).

Factors Affecting Iontophoretic Delivery

Iontophoretic delivery depends on several factors including the current density and time of the application of current. Formulation factors such as pH of the formulation and drug concentration are also very important. Generally, iontophoretic transport increases as the current or drug concentration increases but it may start to plateau at a certain level. The pH of the formulation may control the charge on the drug and may also affect the charge on the skin, in turn affecting the electro-osmotic flow. The resulting effects on iontophoretic transport need to be

evaluated on a case-by-case basis, depending on the physicochemical properties of the drug (Kalia *et al.*, 2004). The charge, size, structure and lipophilicity of the drug will all influence its transport. Biological factors relating to the skin will be less important compared to passive (no enhancement) skin transport but can still influence delivery.

Generally, the current is applied using reversible electrodes such as silver/silver chloride which do not cause electrolysis of water. There is competition among all the ions present in the system to carry the applied charge. Therefore, competitive ions should be minimised to increase transport efficiency, although the transport efficiency will remain less than 100%. Unlike passive transdermal transport, iontophoretic transport predominantly takes place via a pore or transappendageal pathway, i.e. via current shunt pathways such as sweat glands or hair follicles.

Applications of Iontophoresis

Iontophoresis can also be used to drive drugs into other tissues such as the eye (Fischer, 2005) or nasal mucosa (Lerner *et al.*, 2004). An ophthalmic electrode can be placed in the lower cul-de-sac of the human eye and the eyelid holds the device in place during treatment (Fischer, 2005). However, this review will focus on the potential of iontophoresis to drive drug molecules into (topical) or across (transdermal) the skin.

Several investigations have been undertaken for both topical and transdermal applications of iontophoresis. Drugs which have been clinically investigated for topical delivery via iontophoresis include dexamethasone and other steroids, lidocaine, non-steroidal anti-inflammatory drugs (NSAIDs), anti-infectives and antiviral agents. In contrast, drugs which have been investigated for systemic transdermal delivery via iontophoresis, with very few exceptions, typically use animal models or are *in vitro* studies across excised animal or human skin. Delivery of drugs such as antihypertensives, buprenorphine, and nicotine via iontophoresis has been investigated, while delivery of insulin and other peptides in animal models or *in vitro* across human or animal skin has been extensively investigated (Banga, 1998). *In vivo* iontophoretic delivery of salmon calcitonin in hairless rats, using a self-contained wearable and disposable iontophoretic patch, has recently been reported (Chaturvedula *et al.*, 2005). Other drugs which have been investigated recently for systemic delivery by iontophoresis include buspirone (Al Khalili *et al.*, 2003), tacrine (Upasani and Banga, 2004) and rotigotine (Nugroho *et al.*, 2004).

Commercialisation of Iontophoresis for Topical Delivery

Iontophoresis has been successfully used in clinic for topical or local delivery of drugs for several decades. Most of these applications in physical therapy involve the use of dexamethasone and lidocaine, which are used to treat local inflammatory musculoskeletal conditions, such as

bursitis, tendonitis, arthritis, carpal tunnel syndrome and temporomandibular joint dysfunction. The drug is applied to the site via an electrode pad which is then hooked up to an external *Walkman*-sized iontophoresis device. Most commonly used devices on the market include examples from **Empi, Inc.** (Dupel®), **lomed, Inc.** (Phoresor®), and **Life Tech, Inc.** (Microphor®) (Hirvonen, 2005). lomed, Inc. received approval for delivery of lidocaine HCl 2% and epinephrine 1:100,000 (Iontocaine® or Numby Stuff) from the US FDA in 1995 under a new drug application (NDA) for local dermal anaesthesia. This was the first FDA-approved drug labelled for use with an iontophoresis device (Fischer, 2005). More recently, last year **Vyteris** (NJ, US) received FDA approval for its NDA for LidoSite™ Topical System, a pre-filled/pre-programmed iontophoretic system for delivery of lidocaine to achieve local analgesia of skin (<http://www.vyteris.com>). The LidoSite™ system comprises a flexible integrated pre-filled patch, wearable battery-powered controller and a custom-designed interconnect module. It can anaesthetise skin within ten minutes at a depth sufficient for all anticipated needle-stick and dermatological procedures (Kalia *et al.*, 2004). Iontophoresis also has applications in the treatment of hyperhidrosis, a condition of excessive or abnormal sweating and in diagnosis of cystic fibrosis.

Integrated iontophoretic patches, which have recently become available from **Travanti** and **lomed, Inc.**, are disposable, single-use, iontophoresis patches, which can be filled with any drug dissolved in water or buffer.

Commercialisation of Iontophoresis for Systemic Delivery

One drug which has been extensively investigated clinically for iontophoretic delivery is fentanyl (Banga, 1998). Last year, **ALZA**, a member of the **Johnson & Johnson** family of companies, received an approvable letter from the US FDA regarding a NDA for an iontophoresis patch for systemic delivery of fentanyl (<http://www.alza.com>). It is now working to address the issues raised in the letter and bring the product to market.

The patch has been shown to have similar pharmacokinetics as intravenous fentanyl infusion and is therapeutically equivalent to a standard regimen of intravenous morphine, the most commonly used modality for postoperative pain control by patient-controlled analgesia. The product is expected to be compact, credit-card sized and self-contained, providing a system that can be applied to the upper outer arm or chest for control of acute postoperative pain. The patient can activate dosing by pressing a recessed button to deliver a 40 microgram dose of fentanyl over the course of ten minutes. The system will then lock out for a predefined period to ensure that the patients do not receive an unsafe number of doses within a defined period. The patch may be useful in other therapeutic areas and, therefore, should be assessed for its appropriateness to use in conditions such as ambulatory surgery, breakthrough cancer pain, and sickle cell crisis (Chelly, 2005).

Iontophoresis also has applications in medical diagnostics. Reverse iontophoresis, as its name implies, can be used for back iontophoretic extraction (by electro-osmotic flow) of a molecule from the body, rather than its forward iontophoretic delivery into the body. This non-invasive sampling of biological fluids can have several applications. A glucose-monitoring device, GlucoWatch G2 Biographer, which uses the principle of reverse iontophoresis, is on the market to monitor glycaemia in diabetes. It is worn like a wristwatch and provides glucose readings every ten minutes. Currently, it has a drawback in that it needs to be calibrated once a day by an invasive 'fingerstick' but efforts are underway to render the technique completely non-invasive (Sieg *et al.*, 2004).

Conclusions

Iontophoresis is a promising technique for the topical and transdermal delivery of water-soluble drugs, for small conventional drug molecules as well as peptides/proteins. The ideal candidate for iontophoretic delivery for peptides/proteins is one with a high isoelectric point and a molecular weight less than 10 kDa. Iontophoresis is already used clinically for topical delivery of drugs such as dexamethasone and lidocaine and is expected to be commercialised shortly for systemic delivery of drugs using self-contained pre-filled wearable patches.

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