Developments of Transdermal Transport System during Skin Iontophoresis and Electroporation

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Abstract— Transdermal drug delivery offers a non-invasive route of drug administration, although its applications are limited by low skin permeability. Various enhancers including iontophoresis, chemicals, ultrasound, and electroporation have been shown to enhance transdermal drug transport. Iontophoresis is the process of increasing the penetration of drugs into the skin by application of an electric current. 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. Electrical energy assists the movement of ions across the skin using the principle "like charges repel each other and opposite charges attract". In this article, we discuss the iontophoresis and electroporation on the stratum corneum of the skin and its application for dermatological conditions.

1. INTRODUCTION

Transdermal drug delivery offers several advantages over traditional drug delivery systems such as oral delivery and injection including elimination of first pass metabolism, minimization of pain, and possible sustained release of drugs. However, transdermal transport of molecules is slow due to low permeability of stratum corneum, the uppermost layer of the skin. Various physico-chemical penetration enhancers including ultrasound, chemical enhancers iontophoresis, and electroporation have been used for enhancing transdermal drug transport. These enhancers increase transdermal transport through one or more of the following mechanisms: i) Increased drug solubility (chemical enhancers), ii) increased diffusion coefficients (chemical enhancers, ultrasound, and electroporation), and iii) provision of additional driving forces (ultrasound, iontophoresis, and electroporation). While all these enhancers have been individually shown to enhance transdermal drug transport, their combinations have been hypothesized to be more effective compared to each of them alone. Specifically, the following combinations have been used for transdermal drug delivery: Chemicals + Iontophoresis, Chemicals + Ultrasound, and Electroporation + Iontophoresis, see also Fig. 1. In addition to increasing transdermal transport, a combination of enhancers should also reduce the severity of the enhancers required to induced by these enhancers depends on their strength. However, the highest strength of the enhancers that can be applied on the skin is typically limited by safety. By combining two or more enhancers, one can reduce the strength of individual enhancers required to achieve the desired enhancement. Hence, a combination of two or more enhancer may not only increase the total enhancement, but can also increase the safety of enhancers. A review literature describing synergistic combinations of various enhancers is presented in this paper. This paper focuses on the effects induced by iontophoresis and electroporation on the stratum corneum of the skin. Even though the mechanism of drug transport is believed to be different, i.e., electrophoresis for iontophoresis and creation of new aqueous pathways for electroporation, the effects on the stratum corneum detected minutes after current application are very similar.

2. PRINCIPLES OF IONTOPHORETIC TREATMENT

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

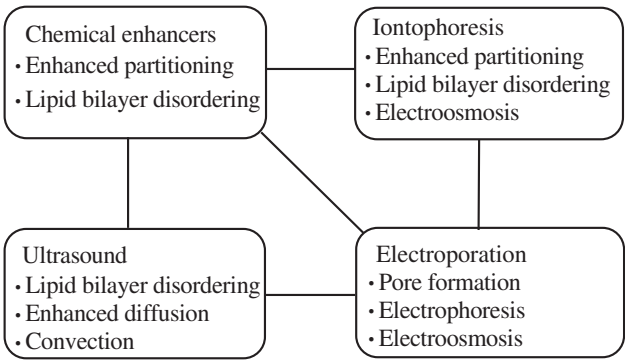


Figure 1: The figure shows possible mechanisms for the synergistic effects between various enhancers. Four enhancers, including chemical enhancers, ultrasound, iontophoresis, and electroporation are listed in each box. Mechanisms responsible for each enhancer are also listed.

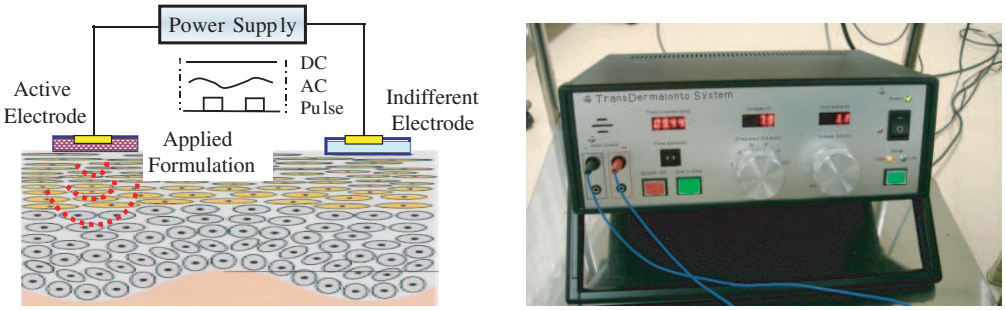
for an appropriate length of time. The electrical current significantly increases the penetration of the drug into surface tissues by repulsion of like charges and attraction of opposite charges. The two classically considered prerequisites for iontophoretic treatment are that the drug must be charged (or modified to carry a charge) and that the disease process must be at or near a body surface. The synergistic effect between chemical and iontophoresis may be attributed to several mechanisms, see Fig. 1.

3. IONTOPHORESIS MECHANISM AND DEVICES

A typical iontophoresis device consists of DC voltage delivery system and electrodes. Wires are then connected between the unit and the active and passive electrodes, and the unit set for current and time. In the iontophoresis process, the current, beginning at the device, is transferred from the electrode through the ionized drug solution as ionic flow. The drug ions are moved to the skin where the repulsion continues moving the drug through the trans-appendageal structures and stratum corneum interstices via the aqueous pores. The larger the electrode surface, the greater the current the device must supply to provide a current density for moving the drug. 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 occurs in a variety of membranes and is in the same direction as the flow of counter-ions. It may assist or hinder drug transport. Since human skin is negatively charged above pH 4, counter ions are positive ions and electro-osmotic flow occurs from anode to cathode. Thus, anodic delivery is assisted by electro-osmosis but cathodic delivery is retarded. Because of the electro-osmotic flow, transdermal delivery of a large anion (negatively charged protein) from the anode compartment is more effective than that from the cathode compartment. 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. The theories behind iontophoresis are straightforward. Coulomb's Law states that "like charges repel" which means that by placing a cationic solution under the anode (+), when a current is applied the positive ions will be drawn toward the cathode (−) electrode. The human body conducts electrical signals very well, as demonstrated by neuronal action. Thus, when an electrode is applied to the skin, the current flows down the path of least resistance and the ionic substance is drawn into the body. Local and systemic drug levels may be achieved when delivering drugs via iontophoresis. However, these levels depend greatly upon the solubility characteristics of each drug and local dermal blood flow. Molecules with more hydrophilic characteristics have been shown to produce systemic levels through their ability to traverse the dermis completely and enter the vasculature. However, lipophilic molecules tend to be attracted to the subcutaneous layer and thus do not move past this stage of the integument. Studies of several therapeutic classes have shown that a class can be stratified by their relative lipophilicity and that overall iontophoresis success follows that stratification. Some of these may be easily treated using iontophoresis, see Table 1. Owing to the advanced nature of transdermal iontophoretic research and development,

Table 1: Common iontophoresis drugs and their charges.

Drug	Charge	Use
Epinephrine	+	Excipient to vasoconstrict
Gentamicin	+	Ear Chondritis, Burn Infection
Hyaluronidase	+	Deep Tissue Hematomas, Edema
Hydrocortisone	+	Inflammation
Lidocaine	+	Pain
Acetic Acid	−	Calcium Deposits
Dexamethasone	−	Inflammation
Ketoprofen	−	Inflammation
Penicillin	−	Burn Infection
Sodium Salicylate	−	Pain



(a) (b)

Figure 2: (a) Schematic of an iontophoretic device. An iontophoretic assembly principally consists of a pair of electrode chambers, which are placed in contact with the skin surface. When the device is powered, the passage of a small electrical current drives positively charged drugs into the skin from the anode and, likewise, negatively charged drugs from the cathode. (b) TransDermaionto System; an iontophoretic delivery system (Atom Giken Co., Ltd., Japan).

these systems are relatively well-characterized and understood. For example, the recently developed TransDermaionto System (Fig. 2; Atom Giken Co., Ltd., Japan) for dermatologic delivery offer iontophoretic platforms, which can be potentially adapted and customized to the local and systemic iontophoretic administration of drugs.

4. ELECTROPORATION MECHANISM AND DEVICES

First used for the introduction of DNA material into cells *in vitro*, the use of electroporation for transdermal delivery was suggested about 15 years ago. Unlike iontophoresis, which employs small currents (transdermal voltages $\leq 20\,\mathrm{V}$) for relatively long periods of time (many minutes to hours), electroporation involves exposure of the skin to relatively high voltages (approx. 30–100 V) for short times, typically 1 to several hundred milliseconds, which in turn create intense electric fields across the thin stratum corneum. Molecular transport through transiently permeabilized skin is thought to result from a variety of mechanisms: Enhanced diffusion through the aqueous pathways produced in the lipid bilayers, electrophoretic movement (for charged species) and, to a small extent, electroosmosis. Although this mode of electrical transdermal enhancement has been shown to be more effective (at least, quantitatively) relative to iontophoresis for several molecules *in vitro*, and to produce significantly elevated levels of transport compared with passive delivery, the limited data from *in vivo* and skin toxicological studies means that its clinical value remains to be established. Owing to the advanced nature of transdermal iontophoretic research and development, these systems are relatively well-characterized and understood. For example, the recently developed Electroporation System device (Fig. 3; Atom Giken Co., Ltd., Japan) for estetic dermatologic delivery offer electroporatic platforms, which can be potentially adapted and customized.

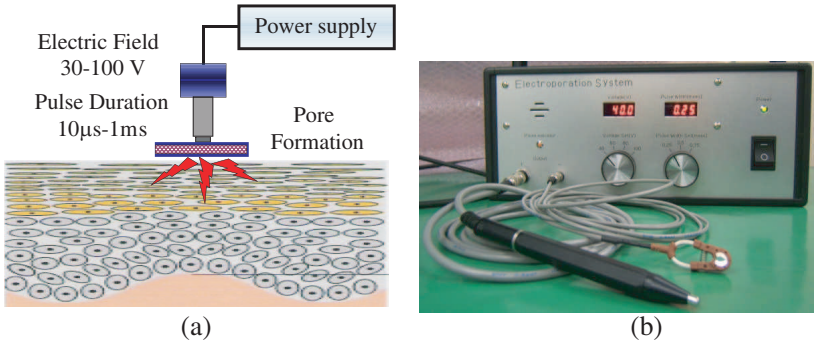


Figure 3: The basic design of electroporation delivery devices. (a) Drug is placed on the skin beneath the electroporation probe. (b) Electroporation System; electrophoretic delivery system for estetic dermatology (Atom Giken Co., Ltd., Japan).

5. DERMATOLOGICAL APPLICATIONS

Iontophoresis has been used for the treatment of various dermatologic conditions. The most successful application of iontophoresis is for the treatment of hyperhidrosis. The basis for hyperhidrosis treatment and its practical aspects have been well described. Currently, the most commonly used conducting medium is tap water because it is safe and effective. Anticholinergic compounds have a longer lasting effect than water, but the side effects of systemic anticholinergic blockade have prevented their wide acceptance. The efficacy and safety of tap water iontophoresis is well documented, but its mechanism of action remains unknown. The most widely accepted hypothesis is that sweating is inhibited by mechanical blockage of the sweat ducts at the stratum corneum level, the depth and severity of the damage being dose-related.

Photodynamic therapy is a promising modality for the management of various tumors and non-malignant diseases, based on the combination of a photosensitizer that is selectively localized in the target and illumination of the lesion with visible light, resulting in photodamage and subsequent cell death. Moreover, the fluorescence of photosensitizing compounds is also utilized as a helpful diagnostic tool for the detection of neoplastic tissue. The two most important interactions governing the transport of light through tissue are scattering and absorption. In photodynamic therapy for skin cancer, 5-aminolevulinic acid (5-ALA) is applied topically to the affected area to be absorbed percutaneously through passive diffusion, and typically requires 4–6 h before performing PDT. In this study, we attempted to reduce the absorption period in PDT by ionizing ALA using direct-current pulsed iontophoresis to treat disease. Five patients who were diagnosed with actinic keratosis (two men and three women in ages ranging from 49 to 94 years, with an average of 79.6 years) and Bowen's disease at the outpatient clinic of the Department of Dermatology, Aichi Medical University, attended this study. Informed consent was obtained from all patients following a full written and oral explanation. Iontophoresis used in the present study was a direct-current pulsed type. When compared with conventional direct-current iontophoresis, pulsed iontophoresis was able to avoid electrode polarization, and drugs could be efficiently applied. For iontophoresis, 20% ALA was dissolved in distilled water, and then current was adjusted based on the area of the functional electrode between 0.25 and 0.50 $\mathrm{mA/cm^2}$. In all subjects, the pulse wave was set at 50 kHz, and ALA was applied to lesion for 10 min. After application, the affected area was washed using distilled water and was shielded from light. One hour after ALA application, a fluorescent spectrometer was used to measure protoporphyrin IX (PpIX) photosensizatizer production. PDT was performed by excimer dye laser and emits 630 nm with pulsed light irradiation at 50 $\mathrm{J/cm^2}$ per session. PDT was repeated three times, weekly (total dose: 150 $\mathrm{J/cm^2}$). One week after the last PDT, a skin biopsy was performed in order to assess the therapeutic effects.

When compared with previous studies, our direct-current pulsed iontophoresis had a higher charge because the concentration of ALA was higher at 20% solution. With the equipment used in the present study, the pulse mode makes it possible to avoid the functional electrode depolarization associated with direct current iontophoresis, and ALA can be efficiently applied. In our study, there were no marked differences in the average PpIX production between 1 h after iontophoresis and > 4 h after occlusive dressing technique. We think that ALA was apparently able to penetrate tumour cells faster with direct-current pulsed iontophoresis when compared with percutaneous absorption based on passive diffusion. Rapid ALA diffusion into cells also quickly depleted the rate-limiting

enzyme, thus accumulating PpIX inside tumour cells. In conclusion, our date suggested that when compared with conventional occlusive dressing technique, PDT could be performed much more rapidly with iontophoresis, resulting in lower a patient burden.

6. CONCLUSION

Various enhancers including chemicals, electric fields, and ultrasound have been used to enhance transdermal drug transport. Although these enhancers have been individually shown to enhance transdermal drug transport, their combinations are significantly more effective compared to each of them alone. This paper focuses on the effects induced by iontophoresis and electroporation on the stratum corneum. Iontophoresis has been explored for many dermatologic and other medical conditions with reports of considerable success. In many conditions, however, these explorations have been limited to a single clinical trial. More rigorous studies are needed to investigate the applications of this mode of therapy.

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