

Development of the Pulsed Direct Current Iontophoresis and Its Clinical Application

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Abstract—The skin is a primary area of body contact with the environment and is the route by which many chemicals enter the body. The delivery of drugs into and through the skin has been an important area of research for many years. Iontophoresis can be defined as the process of increasing the rate of penetration of ions into or through a tissue by the application of an external electric field across the tissue. Impedance spectroscopy was used to investigate the electrical response of skin to different ions, applied currents and fields. The stratum corneum shows two important electrical features. First, it tends to become polarized as an electrical field is applied continuously. Second, its impedance changes with the frequency of the applied electrical field. To avoid the counterproductive polarization, the current should be applied in a periodic manner, which is called pulsed direct current. The pulsed direct current generating iontophoretic delivery system was developed. In the state of on, charged molecules are delivered by the iontophoretic diffusion process into the skin. A non-parenteral method for the delivery of macromolecules was developed by using a pulse direct current mode iontophoretic technique.

1. Introduction

Medical diagnosis and in-patient drug monitoring rely upon the detection and quantitation of endogenous and exogenous bioactive chemicals. Currently, such analysis is predominantly based upon blood sampling which is achieved invasively via needle. The inconvenience and limitations of this procedure are well-known; patients, on the whole, would rather not be injected, the frequency and amount of sampling is constrained, successful intravenous access in geriatric and pediatric patients may be difficult, and there are risks to both patient and sampler. The potential benefits of alternative, noninvasive sampling procedures for chemical exposure assessment and continuous drug monitoring have been described. One approach involves collection, via the skin, of molecules circulating systemically. A major difficulty, however, with this idea is the characteristically very slow and variable passive permeation rates of chemicals across the skin. Indeed, experiments examining the outward migration of theophylline revealed little correlation between sampled amounts and drug levels in the body. Additionally, it was necessary to collect samples over extended periods of time, a significant potential drawback. To circumvent these problems, the application of iontophoresis to enhance sampling efficiency has been examined. Iontophoresis employs an electrical potential gradient to promote the penetration of ionizable molecules across the skin [1–3]. The current uses of the technique are the treatment of dermatology and aesthetic dermatology. In this paper, we have investigated the efficiency of a pulse waveform in the iontophoretic delivery of insulin to achieve blood glucose control and compared the results with a simple direct current iontophoretic delivery system.

2. Theoretical Consideration

The skin of an average adult body covers a surface area of $\sim 2\text{m}^2$ and receives about one-third of the blood circulating through the body. It is one of the most readily accessible organs on the human body. The skin is divided into three layers: the epidermis, the dermis, and the subcutaneous tissue. The epidermis is the outermost portion of the skin and is composed of stratified squamous epithelium. The epidermal thickness varies from $50\ \mu\text{m}$ on the eyelids to 1.5mm on the palms and soles. The innermost layer of the epidermis consists of a single layer of cuboidal cells called basal cells. These cells differentiate and migrate towards the skin surface. The outer layer of the epidermis is called the stratum corneum, which is composed of flattened and dead cells. As they migrate to the skin surface, the cells become more stratified and finally form the cornified layer of the stratum corneum. The skin is known to produce a large impedance to charged molecules as they are driven through the skin by an applied electrical field. The electrical properties of the skin are known to be dominated by the least conductive stratum corneum. Under the influence of electric current, ionic species or charged molecules are driven across the skin, possible through the shunt pathways or intercellular spacing in the stratum corneum, since the skin is likely to be perturbed during iontophoresis, which may remove or disrupt

the intercellular lipids, resulting in the formation of artificial shunts. Iontophoresis facilitated skin permeation flux of an ionic species can be described by an equation consisting of the following three components [4–5]:

$$J = J^p + J^e + J^c \quad (1)$$

where the first term on the right-hand side is the passive skin permeation flux, given by

$$J^p = K_s D_s \frac{dC}{h_s} \quad (2)$$

the second term is electric current driven skin permeation flux

$$J^e = \frac{Z_i D_i F}{RT} C_i \frac{dE}{h_s} \quad (3)$$

and the last term is the convective flow driven skin permeation flux

$$J^c = k C_s I_d \quad (4)$$

in which K_s is coefficient for interfacial partition from donor solution to stratum corneum, C_i is donor concentration of ionic species, C_s is concentration in the skin tissue, dE/h_s is electric potential gradient across the skin, dC/h_s is concentration gradient across the skin, D_i is diffusivity of ionic species I in the skin, D_s is diffusivity across the skin, I_d is current density applied, Z_i is electric valence of ionic species I , k is proportionality constant, F is Faraday constant, T is absolute temperature, and R is gas constant. This equations describes the flux of an ion under the influence of both a concentration gradient and an electrical field.

Table 1: Some representative iontophoretic delivery systems.

Iontophoretic system	Drug delivery mode
<i>Direct current mode</i>	Continuous drug delivery under constant intensity of direct current
<i>Pulse current mode</i>	
(a) Depolarizing pulse Iontophoresis system	Continuous drug delivery under constant application of pulse current
(b) Periodic iontotherapeutic system	Programmed drug delivery under periodic applications of pulse current with constant intensity

Essentially, two types of iontophoresis have been investigated: the earlier one uses a simple direct current mode, while the more recent one utilizes the pulsed direct current mode in shown Table 1. An iontophoretic drug delivery system is composed of four basic components including a battery, control circuitry, electrodes, and reservoirs. The component configuration is schematically illustrated in Figure 1. The battery supplies the required energy to power the control circuitry which, subsequently, controls the electric potential applied to the electrodes. Because drug delivery is roportional to the current flowing through the body, most iontophoretic transdermal drug delivery control circuits utilize some type of current source to compensate for the difference in skin resistance from person to person. A battery and a single resistor is a simple current regulator, but regulation is effective for only small resistance variations. Active current regulators automatically adjust their operating characteristics in response to a broader range of resistances and therefore are preferred for iontophoretic transdermal drug delivery applications since the resistances from person to person or from site to site can vary significantly. The electrodes of an iontophoretic device are in direct electrical contact with the reservoirs, and together they determine the electrochemical reactions that occur at the anode and cathode. These reactions are particularly important to

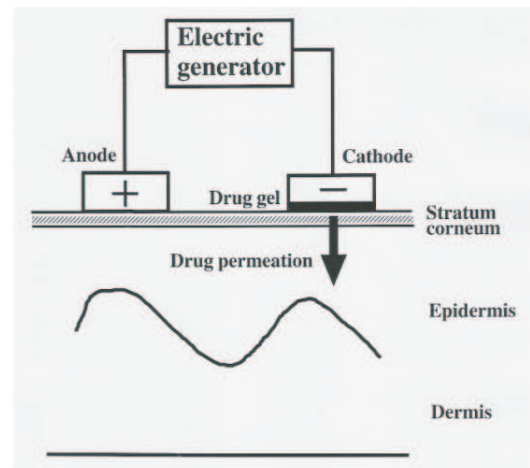


Figure 1: Schematic illustration of the major components of an iontophoresis system.

consider when designing iontophoretic devices for the delivery of drugs over extended periods of time. A better choice of electrode materials would be titanium or silver for the anode and chloridized silver for the cathode.

3. Materials and Methods

Tissue samples were obtained from freshly rats skin. All tissues of exactly known time history were prepared in the same way. A cylinder of diameter corresponding to the diameter of the electrode was excised from the bulk of the test tissue. It was then inserted into a plastic tube and a microtome was used to cut tissue discs of the desired thickness equal to the distance between the electrodes. The dielectric measurements were performed using automatic swept-frequency network and impedance analyzer. The frequency range 5 Hz to 10 MHz was covered by an HP-4192A impedance analyzer. Open-ended co-axial probe were used to interface the measuring equipment with the samples in all cases. The probe is characterized by a fringing capacitance and conductance which are functions of its physical dimension and can be measured with the impedance analyzer. In addition there are stray capacitive and inductive elements that have to be normalized. Figure 2 is a schematic diagram of the experimental arrangement [6]. For each set of measurements new samples were excised from the bulk of the tissue, which was sealed to avoid tissue drying and stored at ambient temperature during the measurement session.

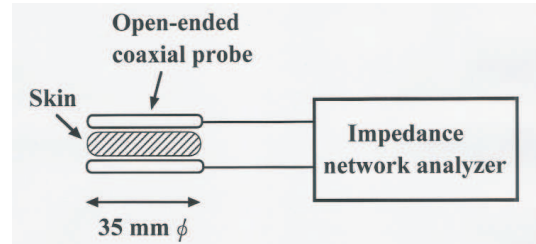


Figure 2: Schematic diagram of the measuring system.

4. Results and Discussion

The condition inside the tissues when adding an electric field to the tissues becomes the index that the complex permittivity of the tissue is important. The real component corresponding to the permittivity and the imaginary component, known as the dielectric loss, corresponds to the dissipative loss associated with the movement of polarisable charges in phase with the electric field. This shows that, as a dielectric dispersion is traversed by changing the frequency of measurement, the change in conductivity is directly proportional to the change in permittivity. This follows from the fact that the total energy in the field is constant and must either be stored or dissipated by the system with which it interacts. The dielectric properties of skin show considerable variability over different parts of the body. The average electrical properties of skin in the range 5 Hz–1 MHz are shown in Figure 3. An interpretation of these properties was approached via a consideration of the inhomogeneous structure and composition of skin and of the way in which this varies from the skin surface to the underlying dermis and subcutaneous tissues. The dielectric properties of skin are largely determined by the stratum corneum, which has a thickness of some 15 μm and consists largely of dead cells [7–9]. As for the complex permittivity, the characteristic to become minimal around 50 kHz was measured.

It may be noted that skin possesses a relatively weak α dispersion, and this relative lack of a significant dispersion in the frequency range 1 Hz–100 kHz is plausibly ascribed to the dead nature and low conductivity of the stratum corneum. It was tentatively suggested that the origin of these dispersions lay in the stratum corneum and was associated with the relaxation of ions surrounding the corneal cells. It is worth drawing attention to the fact that the electric impedance of those parts of the skin at which the points and meridians of acupuncture are located is significantly less than that of the surrounding tissue, a fact which may be presumed to be of diagnostic value and may plausibly underlie the mechanism by which signals are transmitted around the body by means of the meridians of acupuncture. Many therapeutic and diagnostic techniques rely upon the application of electrical fields or

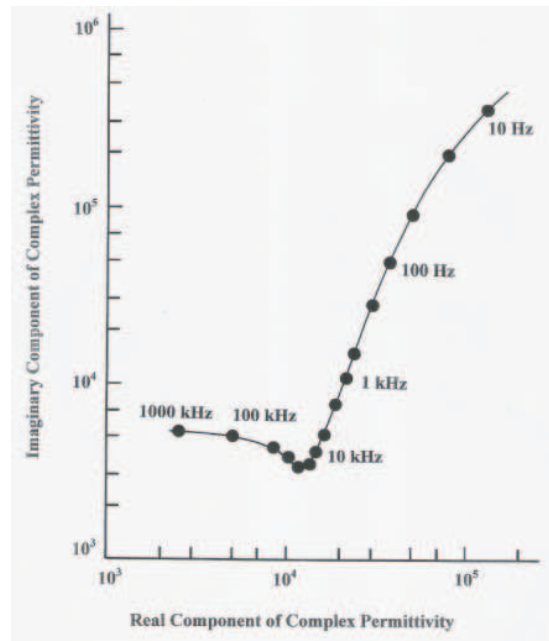


Figure 3: A typical example of the dielectric constants of skin as a function of frequency.

the measurement of electrical properties. Since skin tissue often constitutes the interface between the biological and electronic parts of the system, its dielectric properties are of some interest and importance. It is worth drawing attention to the fact that the electric impedance of those parts of the skin at which the points and meridians of acupuncture are located is significantly less than that of the surrounding tissue, a fact which may be presumed to be of diagnostic value and may plausibly underlie the mechanism by which signals are transmitted around the body by means of the meridians of acupuncture. Therefore, the complex permittivity is the important index that the energy absorption which is consumed in the tissue can be discussed.

Skin manifests large impedance to charged molecules which are driven through the skin under an applied electrical field. The electrical properties of the skin are dominated by the stratum corneum which is considered to be the least conductive layer of the skin. Stratum corneum consists of multilayers of cornified cells. These electrically insulated horny cells are continuously replenished by the slow upward migration of cells from the basal cell layer of the stratum germinativum. An analogous equivalent circuit of skin impedance is shown in Figure 4. It consists of a resistor, R_{sc} , and a capacitor, C_{sc} , existing in parallel in the stratum corneum, which is then in series with the resistor, R_{vs} , in the viable skin. The magnitude of R_{sc} is rather large, and can range from 10–20 $k\Omega cm^2$ in animal skin to 100–5000 $k\Omega cm^2$ in human skin, while R_{vs} is relative small in magnitude and is in the range of 0.1–1.0 $k\Omega cm^2$. The stratum corneum shows two important electrical features: first, it is polarized by the electrical field, and second, its impedance changes with the frequency of the applied electrical field. When an electrical field with direct current is applied in a continuous manner to the skin, an electrochemical polarization develops rapidly in the capacitor. It often operates against the applied electric field and greatly decreases the magnitude of effective current across the skin.

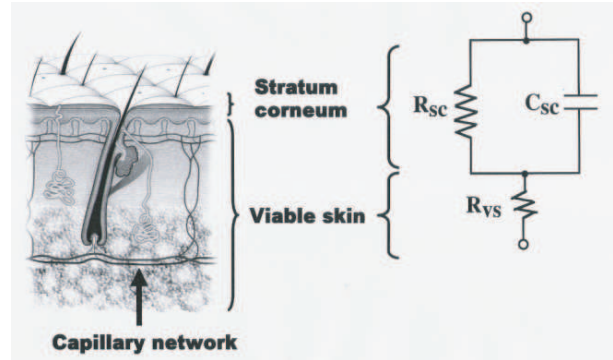


Figure 4: Diagrammatic illustration of the analogue equivalent circuit of skin impedance.

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To avoid the polarization of the stratum corneum, a pulse direct current can be used [10]. The pulse mode is a direct current voltage which periodically alternates with the “on” and “off” of the applied voltage in Figure 5. In the state of “on”, charged molecules are forced into the skin and the stratum corneum soon becomes polarized; while in the state of “off”, no external stimulation is present and the stratum corneum becomes depolarized. The on/off ratio controls the proportion for polarization and depolarization process in each cycle. The current output generators were built in-house. The pulsed-current unit was designed to provide adjustable peak voltages from 0 to 20 V and variable frequency from 0 to 300 kHz. The wave form used in the pulsed-current unit is also shown in Figure 5. The on/off ratio or the percent duty could be varied from 0 to 70%. This unit had 15 channels and a display that provided the average current readout for each channel. This average current readout is the current averaged over the cycle. At a setting of 40 kHz duty, for example, the duration of each pulse would be 25 μs , but at a setting of 30% duty, the pulse would be on for 7.5 μs and off for 17.5 μs . In some experiments, a pulsed-current unit with a single output channel and a fixed frequency and percent duty was used. When an ideal on/off ratio is selected, every new cycle starts with no residue polarization left in the skin from the previous cycle, i.e., the effect of polarization is eliminated.

The energy (E) required to overcome the penetration barrier, stratum corneum, can be expressed by:

$$E = \int [V(t)i(t)]dt = \int [i(t)^2 R_t(t)]dt \quad (5)$$

where $V(t)$ and $i(t)$ are the voltage and current applied respectively and R_t is the impedance of the skin. As can be seen from Eq. 5, less energy will be required to overcome the barrier when the skin impedance is reduced. This may be achieved by applying the current with proper frequency and on/off ratio. Therefore, it is essential to select optimum pulse mode parameters to attain the best facilitating effect of iontophoresis for a particular drug or a dosage form.

Diabetes mellitus is a chronic systemic disease in which the body either fails to produce or fails to respond to the glucose regulatory hormone insulin. Insulin is required in order for cells to take up glucose from the blood, and in diabetics, a defect in insulin signaling can give rise to large fluctuations in blood glucose levels unless proper management techniques are employed. Insulin, a protein hormone containing 51 amino acid residues, has a molecular weight of approximately 6,000 daltons and an extremely short biological half-life of

less than 30 minutes. In healthy humans, it is secreted by beta cells in the Langerhans islet of the pancreas in response to an increase in blood glucose level to facilitate the process of glucose utilization for either energy or storage. In patients with diabetes mellitus, however, the capacity of the pancreas to supply insulin in response to the increase in blood glucose level is impaired. For the control of diabetes mellitus, insulin must be supplied externally by subcutaneous injection at a dose of 10–20 units three to four times a day. Experiments were conducted in a skin to study the feasibility of facilitating the transdermal delivery of insulin across the freshly excised abdominal skin of rats by applying iontophoresis with a pulsed direct current. The results demonstrated that the skin permeation rate of insulin thus applied is enhanced substantially as compared to that achieved by passive diffusion alone. The insulin data summarized in Figure 6 were generated using the iontophoresis shown in Figure 5. The use of iontophoresis results in the typical sigmoidal dependence of receptor concentration on time. The time required to achieve a steady-state receptor concentration is determined by the receptor volume and flow rate of the receptor solution. For the *in vivo* conditions used in the insulin study, time to achieve a steady-state concentration was about 2 hours for all currents, as shown in Figure 6.

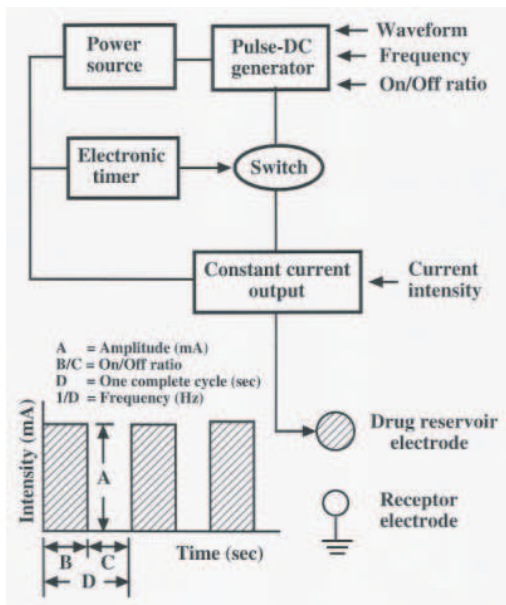


Figure 5: Diagrammatic illustration of the transdermal periodic iontophoresis system. Diagram of a pulse waveform profile, where A is the amplitude of a current intensity (mA), B/C are the on/off ratio, D is the duration (s) of a complete cycle and so $1/D$ is the frequency.

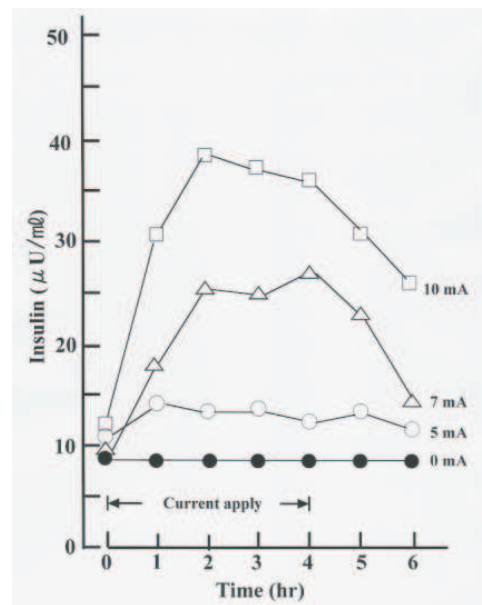


Figure 6: *In vivo* skin permeation profiles of insulin under the iontophoresis facilitated permeation by the pulse current.

The cumulative amount of insulin permeating through the skin increases with time during the period of transdermal periodic iontophoretic system treatment and gradually returns to the skin permeation profile by passive diffusion after termination of the treatment. Also plotted in Figure 6 for comparison is the rate profile of insulin permeation. Analysis of the skin permeation rate profile suggests that the pulsed direct current iontophoresis facilitated transdermal transport of drug molecules consists of four phases: (i) the facilitated absorption phase, in which the skin permeation of drug molecules is enhanced by iontophoresis treatment and the skin permeation rate linearly increases with the time of treatment; (ii) the equilibrium phase, in which the skin permeation rate has reached a plateau even though iontophoresis treatment is continuously applied; (iii) the desorption phase, in which the skin permeation rate decrease linearly with time immediately after the termination of iontophoresis treatment and the drug molecules already delivered into the skin tissues are desorbed into the receptor solution; and (iv) the passive diffusion phase, in which the skin permeation rate returns to the baseline level as defined by passive diffusion. The transdermal periodic iontophoretic system facilitated skin permeation rate of insulin was observed to increase linearly with the current density of pulsed direct current applied, but in a non-linear manner with the duration of transdermal periodic iontophoretic

system application time. The therapeutic response of insulin obtained in the present study indicates that, in the presence of a facilitated transport, it may be possible to topically administer high molecular weight substances, including other peptides and/or proteins, for systemic therapy. The present work has demonstrated that the iontophoresis technique may provide a convenient means for the systemic delivery of insulin without the use of a hypodermic needle. The feasibility of optimizing the plasma concentration of the drug by either controlling the time of application and/or regulating the magnitude of current, or alternatively, by the use of a pulse current rather than a direct current, needs further investigation.

5. Conclusions

A non-parenteral method for the delivery of macromolecules such as insulin was developed by using a pulse direct current mode transdermal iontophoretic technique. The intensity of current, frequency, on/off ratio and mode of waveform were found to play an important role in the transdermal iontophoretic delivery of insulin. More extensive investigations on various aspects of this system are necessary to obtain optimum parameters of pulse direct current mode for transdermal iontophoretic delivery of dermatology and cosmetic science.

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