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Volume 104  
Issue 5  
May 2009  

www.sensorsportal.com

ISSN 1726-5479

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International Frequency Sensor Association (IFSA).
Effect of Low Frequency Pulsed DC on Human Skin in Vivo: Resistance Studies in Reverse Iontophoresis

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Received: 22 March 2009 /Accepted: 19 May 2009 /Published: 25 May 2009

Abstract: Instrumentation suitable for continuous monitoring of reverse iontophoresis in vivo in human subjects is developed. It supplies the required current and acquires the potential profile of the skin during reverse iontophoresis. Potential profiles showed that skin resistance decreases with the application of current. Experimental results revealed that the application of pulsed DC tends to make the reverse iontophoresis more effective by enhancing the flow of analytes which is proved by the fact that resistance decreases and stabilizes faster in comparison to the one with direct current reverse iontophoresis. The paper emphasizes the importance of selecting an appropriate duty cycle and frequency for reverse iontophoresis. Duty cycle around 95 % and frequency of 250 mHz are good for low frequency reverse iontophoresis. Effect of reverse iontophoresis on the skin recovery is observed by monitoring the potential profiles at the end of the process. In all the reverse iontophoresis experiments, safety of the patient is ensured by fixing a compliance voltage level. Copyright © 2009 IFSA.

Keywords: Pulsed DC, Reverse iontophoresis, Duty cycle, Skin resistance, Potential

1. Introduction

Skin has been seen as a possible route for administering drugs into the human body historically and also as a means of non-invasive sensing and diagnosis. Many attempts have been made in the past few decades to administer drugs across the stratum corneum of the skin into the systemic circulation. Advances in drug delivery systems owe to the growing research in the fields of iontophoresis, sonophoresis and associated methods for delivery and non invasive sensing.
Iontophoresis is a process by which drugs are administered into the body by the application of electromotive force. During iontophoresis, for delivering a positively charged drug, it is dissolved in the electrolyte surrounding the electrode of similar polarity. On application of an electromotive force the drug is repelled and moves across the stratum corneum towards the cathode, which is placed elsewhere on the body. Communication between the electrodes along the surface of the skin has been shown to be negligible, i.e. movement of the drug ions between the electrodes occurs through the skin and not on the surface [1]. Similarly drugs/analytes could be extracted across the stratum corneum by the reverse process called the Reverse Iontophoresis. As the movement of drugs is through the skin, skin behavior is of a very huge significance in non invasive sensing via the skin route. The studies on iontophoresis revealed that a few combination strategies could improve the iontophoretic drug delivery. These include using Iontophoresis in combination with some of the other methods like electroporation, sonophoresis and in conjunction with chemical enhancers, micro needles, ion exchange materials. It reported that the skin irritation associated with iontophoresis has been addressed by several studies and it is an issue preventing wide application of the technology [1].

High voltage pulses for small duration were also used for electrical creation of aqueous pathways across the skin for skin electroporation [2]. Impedance of the skin reduces highly due to the application of high voltage pulses and recovery of skin after electroporation takes a very long time. As the time of application of the HV pulse was increases, recovery becomes difficult. Studies were useful to know the skin behavior and also in analyzing the blood flow with HV pulse applied [3]. It was also felt that application of HV pulses increases the skin capacitances which gives the impression of changes in skin lipid structure [4], therefore skin recovery is a problem. Similarly, attempts on skin impedance studies were made to see the effect of iontophoresis and permeation enhancers on female Yorkshire pigs [5] and was found that skin resistance is a measure of permeation of analytes. Similar studies were done on human skin and skin impedance models were proposed [6-7]. It was also proposed that the skin resistance can be used not only as a compensation factor but also as a representing parameter for skin status, such as severe perspiration or stabilization phase. Invitro studies in the past revealed that the skin resistance change implies many phenomena during the reverse iontophoresis, particularly the skin porosity. Therefore, it should be directly related to the amount of extracted solute [8].

Therefore, skin resistance is seen in recent times as an important factor which could be used in monitoring the drug delivery as well as in non invasive sensing of analytes. The higher rate of decrease in skin resistance implies the higher rate of extraction and stabilization during reverse iontophoretic extraction. Therefore, instrumentation suitable for monitoring reverse iontophoresis and skin resistance behavior is developed.

2. Experimentation

Fig. 1 shows the schematic of the instrument developed for Reverse Iontoporetic monitoring. An AC-DC current source (Keithley 6221) is used for application of direct and pulsed direct currents. It has features relating to very stable current delivery with a safety option provided in the form of compliance level settings. It is interfaced to the computer through GPIB (IEEE 488). A multimeter (Keithley 2002) is used to acquire the potential (resistance) information during the course of reverse iontophoresis experiments. More finer details of instrumentation are documented in M.Sc (Engg) thesis [9].

Ag/AgCl based gel electrodes are used for current delivery during reverse iontophoresis. These electrodes are used as they are inert, work at low voltage, provide a stable environment for the analytes and minimize the transport of toxic species to the skin. The electrodes are placed on the forearm of the subject at a distance 16mm apart. LabVIEW 7 is used for programming and controlling the
instruments. Front end of the instrument developed for monitoring the reverse iontophoresis is shown in Fig. 2.

![Diagram](image)

**Fig. 1.** Schematic of the instrumentation for monitoring Reverse Iontophoresis.

The front end consists of fields to input reverse iontophoretic parameters like current amplitude, frequency, duty cycle, number of samples. It also displays the potential profile, instantaneous potential values along with the statistical data required for analysis. Provision exists on the front end to store the data into the memory by creating an appropriate directory. Fig. 2 is a snapshot obtained while the reverse iontophoresis experiment was conducted on human in vivo for a current of 100 µA with a compliance level of 20 V.

![Screenshot](image)

**Fig. 2a.** Front End of Reverse Iontophoresis Monitor. Pulsed DC Reverse Iontophoresis Potential profile is displayed on the waveform chart.
Constant current reverse iontophoresis experiments are conducted with a reverse iontophoretic current of 20 µA with a compliance level of 10 V. Potential difference between the electrodes is monitored throughout the reverse iontophoretic extraction process to get the idea of the resistance profile of the skin with current delivery. Effect of Reverse Iontophoresis on the skin is studied by monitoring the potentials continuously after the reverse iontophoretic current delivery is stopped.

Later, similar experiments are conducted with pulsed DC. Pulsating direct current at very low frequencies (mHz) is applied to study the potential (resistance) profiles, time to obtain the steady potential profile, there by indicating the steady flux of analytes with current delivery. The behavior of skin throughout and after the process is also monitored. Pulsed DC Iontophoresis experiments are conducted with pulsed direct current varying the duty cycle. Similar experiments are conducted at very low frequencies of input pulsed current in the range 1 to 500 mHz. Very low frequency studies are taken up to understand the resistance behavior of the skin (as skin capacitances dominate at the high frequencies and in the case of HV Pulses for a very short duration).

3. Results and Discussion

Fig. 3 shows the potential profile of the skin acquired during constant direct current reverse iontophoresis with an input current of 20 µA across the Ag/AgCl electrodes on the skin. Decrease in skin resistance is observed with time of application of current. This implies that there is an increase in the extracted flux of analytes [8].
Fig. 3. Potential Profile of Constant Direct Current Reverse Iontophoresis.

This result is in accordance with the in vitro studies reported in the literature [5, 6, 8]. Potential profile stabilizes to a constant value only after the application of current for a very long duration. Reddening of the skin under the electrodes is observed when current is applied for a long duration.

Fig. 4 shows the potential profile of the skin when pulsed DC is applied. It is observed that the potential falls with the application of pulsed DC. The rate of decrease in resistance is higher and the time for stabilization of the potential is less than that for direct current reverse iontophoresis. The plot clearly shows the fall in potentials and the behavior of the skin closely with each pulse applied. Application of the pulsed current allows the skin to relax and thereby avoids the polarization of the skin towards a particular charge occurring due to continuous direct current.

Fig. 4. Pulsed DC Reverse Iontophoresis Potential Profile.
Fig. 5a, 5b, 5c, 5d, 5e and 5f show the responses with pulsed DC applied with duty cycles of 70 %, 75 %, 80 %, 85 %, 90 % and 95 % respectively. These studies revealed that by controlling the ON and OFF duration of the pulse, time for stabilization of reverse iontophoresis can be calculated and controlled. Pulse duty cycles around 95 % are found to be the best for pulsed DC Reverse Iontophoresis at low frequencies.

Fig. 5. Pulsed DC Reverse Iontophoresis at various Duty Cycles.
Fig. 6 gives the stabilization time for various duty cycles. Fig. 6 shows that, as the duty cycle is increased to 95%, the rate of stabilization increased and the settling time for the process decreased. Potential profiles for the low frequency reverse iontophoresis are shown in Fig. 7. The effect of very low frequency pulsed DC (mHz range) on reverse iontophoresis is shown in Fig. 8. It is observed that frequency of 250 mHz is good for low frequency reverse iontophoresis. The skin recovery after the application pulsed DC reverse iontophoresis are shown in Fig. 9 and Fig. 10 for various duty cycles and the low frequencies.

The skin recovery profiles follow an exponential decay pattern as shown. These potential decay profiles are just due to the skin getting back to normalcy after being charged because of application of pulsed DC. During the course of experiments it was also observed that the recovery takes longer time as the magnitude of pulsed current is increased. Fig. 11 shows the recovery patterns of the skin after the reverse iontophoresis experiments with input currents of 100 µA and 125 µA. It has also been found that the problems like irritation and reddening of the skin caused by the application of constant DC current iontophoresis for long duration during continuous monitoring are solved by the pulsed DC application as the skin gains time for recovery with the OFF time in the pulse application.

Experimental results revealed that the application of pulsed DC tends to make the reverse iontophoresis more effective by enhancing the flow of analytes which is proved by the fact that resistance values (voltage across the electrodes divided by the applied current) decreases rather quickly with a higher slope to start with and finally reaching a steady value quickly in comparison to the one with constant current reverse iontophoresis.

For the studies conducted in vivo in human subjects, it was found in general that the fall in potential closely follows a third order polynomial varying with time before finally settling to a near constant value. The polynomial is of the form \(a + bx + cx^2 + dx^3\) with values of \(a, b, c, d\) ranging from 8 to 9.5, 0 to -0.003, 6 \(E^{-7}\) to 8\(E^{-7}\), -5.5\(E^{-11}\) to -8\(E^{-11}\) (\(E\) stands for power of 10) respectively for pulsed DC reverse iontophoresis, where \(x = t/2\), \(t\) denotes the reverse iontophoresis time.
Fig. 7. Pulsed DC Reverse Iontophoresis at low frequencies.
Fig. 8. Effect of low frequency pulsed DC on reverse iontophoresis.

Fig. 9. Skin Recovery Profiles after Low frequency Pulsed DC Reverse Iontophoresis.

Fig. 10. Skin Recovery Profiles after Pulsed DC Reverse Iontophoresis for various duty cycles.
4. Conclusions

It is observed that Pulsed DC reverse iontophoresis is better than direct current reverse iontophoresis for in vivo applications. Skin resistance decrease and the potential profile stabilization is faster for pulsed DC reverse iontophoresis. Pulse duty cycles around 95% are good for Pulsed DC reverse iontophoresis. Frequency of around 250 mHz is good for low frequency reverse iontophoresis. Recovery of the skin after reverse iontophoresis is also monitored with the present setup. Recovery depends on the magnitude of the applied reverse iontophoretic current. Pulsed DC can be applied for extraction of various analytes for diagnostic applications and can be used to study the effects of reverse iontophoretic extraction on the skin health. Further improvement of the system with inbuilt capabilities to monitor the skin impedance status by multi frequency impedance spectroscopy will lead to the self calibrated reverse iontophoresis systems for measurements and continuous monitoring.

References


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Guide for Contributors

Aims and Scope

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