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Biphasic Transdermal Iontophoretic Drug Delivery Platform

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Abstract— **Transdermal iontophoresis is an active drug delivery method that has the potential to transform treatment of conditions such as acute pain that require a succession of on-demand metered-dose drug deliveries. However, current monophasic iontophoresis methods fail to meet these requirements due to their inability to halt the passive diffusion of active agents when therapy is not required. We have developed a biphasic iontophoretic system to overcome these limitations. The viability of this system was assessed in an in vitro porcine skin preparation using $FeCl_2$ (127 Daltons), a charged molecule which can undergo both active and passive transdermal diffusion. The transport properties of the system were modeled using a Fourier Transform-derived optimum estimate transfer function. Using this model, experimental results showed good correlation to predicted values for both cumulative dose (R^2=0.912, n=10), and density dose (R^2=0.802, n=10). Results also showed the ability to effectively deliver the compound during active periods while minimizing delivery during inactive periods. While preliminary, our results suggest biphasic iontophoresis is a viable means of delivering on-demand drug therapy while minimizing unwanted off-demand delivery.**

Keywords- **Iontophoresis, biphasic, drug delivery, on-demand.**

I. Introduction

On-demand metered dose drug delivery is important for the treatment of acute conditions such as pain, migraine headaches, and chemotherapy-induced nausea, which require frequent doses with a rapid onset of action. The current oral drug treatments for these conditions are not ideal due to their delayed onset of action if taken during an acute event along with the systemic side effects that the patient experiences due to prophylactic therapy [1].

Groups have attempted to use monophasic DC iontophoretic devices to overcome these shortcomings but have had limited results due to the inability to inhibit the passive diffusion of the drug [2]. Drugs such as opiates used to treat these acute episodic conditions are associated with intolerable adverse effects: respiratory depression, impaired cognitive function, etc. Thus continuous exposure to these compounds is not desirable [3].

A biphasic iontophoretic system that has the capability to both actively drive and inhibit the transport of drug through the stratum corneum has the potential to overcome these limitations, is presented.

Several other techniques also deliver agents transdermally, e.g., sonophoresis, electroporation, cavitational ultrasound, microneedles, and they hold tremendous promise for future developments [4] but unlike the biphasic iontophoretic system these methods are only capable of a unidirectional drive of the active agent and rely on passive methods for the inhibition phase.

II. Methodology

A. System Description

The developed system consists of four parts: active electrode, passive electrode, iontophoresis system and programmer.

1) Active electrode: Was constructed by using a DuPel Model #198809-001 (Empi, Inc., Clear Lake, SD, USA) electrode with the buffering agent removed and replaced with a teabag filled with two sheets of 3M gauze with 4.0 ml of solution. The solution was prepared by dissolving 1.2g of $FeCl_2$ (Sigma-Aldrich, St. Louis, MO, USA) and 300 mg of Poly-Ethylene Oxide (PEO, Mol wt. 100k) into 4 ml of DI water. The active electrode area was 13.3 cm^2.

2) Passive electrode: Was constructed by using a DuPel Model#198809-001 electrode with the buffering agent removed and replaced with a teabag filled with two sheets of 3M gauze and 300 mg of Polyethylene Oxide (PEO) with 4 ml of DI water added. The active electrode area was 13.3 cm^2.

3) *Electrode leads:* Consisted of standard set of 080 18" Snap lead bundles Model # 23100-PAC (Black) & 23120-PAC (Red) (Bioconnect, San Diego, CA, USA).

4) Iontophoresis system: Consisted of a custom made unit that was controlled by a MSP430F428 (Texas Instruments, Dallas, Tx, USA) microcontroller. This microcontroller coordinated the activities between the switch states of an H-bridge circuit in conjunction with a variable current source. The H-bridge had a programmable voltage rail with a resolution of ~650mV steps and a maximum compliance voltage of 80V. The variable current source had a programmable current

target with a resolution of ~40μA with an upper limit of 5 mA. The microcontroller was able to update these values at a rate of 5Hz along with measure and store their values with a time stamp for data archival purposes. Two AA batteries were used to power the system. These batteries were capable of providing up to 40 hours of operation under a standard therapy profile. Fig.1 shows a picture of the system along with a simplified block diagram of the internals.

5) Programmer: Consisted of a personal computer that interfaced to the iontophoresis system via a USB cable. The application code used to program the device was written in TCL/TK. This program enabled specification of the therapy pulse duration and current value along with the inhibit pulse duration and current value. It was also capable of specifying the total therapy duration. In addition, the programmer could retrieve the data stored in the unit for analysis.

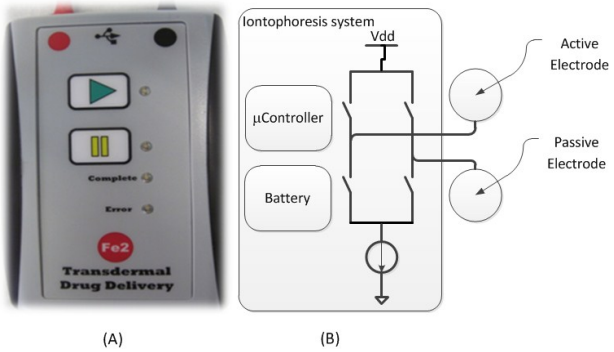

Fig. 1. (A) Picture of actual transdermal delivery device. (B) Block diagram of major internal components of transdermal delivery device

B. Experimental Setup

Ten in-vitro test chambers were constructed out of block PTFE and filled with 120ml of Hanks Buffered Salt Solution (HBSS). Freshly excised abdominal skin from a male Yorkshire pig (35 kg) was sectioned into 10 (100 mm × 175 mm) pieces. Yorkshire pig skin was used as it has been shown to closely mimic the properties of human skin for permeability but has been shown to be less predictable for lag time measurements [5].

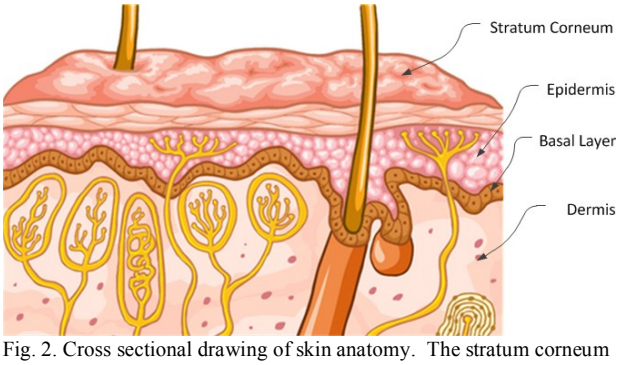

Fig. 2. Cross sectional drawing of skin anatomy. The stratum corneum is the top layer that represents the primary barrier. The next layer is the epidermis and then the basal layer. The last and by far the thickest layer is the dermis.

The subcutaneous fat beneath the dermis layer of the skin was removed so that only the stratum corneum, epidermis, basal layer and dermis layers remained (Fig 2), with an average thickness of 3 mm. The skin was then shaved and inspected for blemishes or scratches that might alter transport. Each test chamber had a piece of skin placed on top. Particular care was taken to not damage the integrity of the skin. The skin was affixed to the test chamber via 1 ¼" clips.

The active and passive patches were both adhesively attached to the pig skin and the patch electrodes were then connected to the iontophoresis system as depicted in Fig 3. All skin irregularities were avoided during this process.

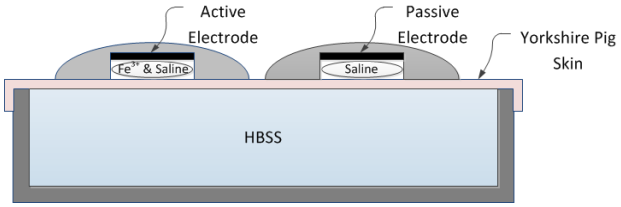

Fig. 3. Schematic representation of experimental chamber

The iontophoresis system was configured to provide a 6-hour therapy session. The first hour of the therapy session consisted of the system in an inhibitory mode with a current value of -3 mA. The second hour of the therapy session was a drive mode with a current value of 3 mA. In hour 3 and 4 the system was in the inhibitory mode with a current value of -3 mA. In hour 5, the system was in a drive mode with a current value of 3mA, and in hour 6 the system was in an inhibitory mode with a current value of -3mA.

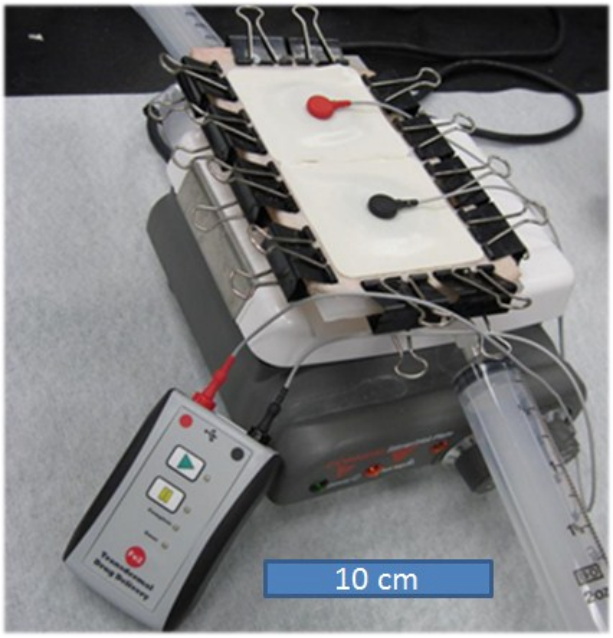

Fig. 4, Photograph of experimental setup showing the transdermal delivery device in the lower left corner, the active electrode in the top center, the passive electrode in the middle center, with the experimental chamber placed on a hot plate.

Upon completion of the therapy, the skin samples were visually examined for irritation and or staining. The samples were then photographed. A photograph of the complete experimental setup is shown in Fig. 4.

The experimental chambers were placed on magnetic stirrer-hotplates to maintain the HBSS solution between 29 °C to 34 °C, which kept the surface of the pig skin between 28 °C to 33 °C [6]. Samples of 1 ml were drawn every 15 minutes from the reservoir, using a 25 gauge needle. An equivalent volume of HBBS solution was replenished to maintain the level in the test chamber. During the data analysis, appropriate correction factors were used to compensate for this fluid replacement.

The concentration of iron was quantified, after the required dilutions, by using a standard colorimetric assay [6]. The samples were added to an acidic buffered reagent containing hydroxylamine, thiourea and Ferene (5, 5' (3-(2-pyridyl)-1,2,4-triazine-5,6-diyl)-bis-2-furansulfonic acid, disodium salt). The acidic pH of the buffered reagent releases the ferric iron, which is then reduced to ferrous form by the hydroxylamine. This ferrous iron then reacts with the Ferene producing a colored complex. The absorption of this ferrous-Ferene complex was then read at 595 nm using a spectrophotometer (Multiscan EX; Thermo Electron Corporation, Vantaa, Finland). The absorption spectrum provided a proportional relationship to that of the iron concentration within the sample. This assay method provides a lower limit of quantification of 50µg/dl.

III. Results

The average of the ten samples was taken for each 15 minute sample period to obtain a mean cumulative density data set. This data set was then used as the measured output of the system to be identified, y(t). The input to the system was the known integral of the active portion of the therapy session, x(t). These sets of data were then used to identify the system transfer function, $h_{est}(t)$. A block diagram of the system is shown in Fig 5.

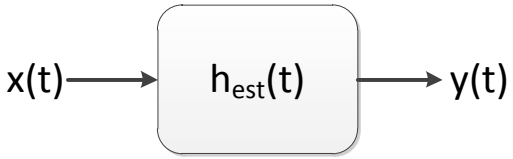

Fig. 5.Simplified block diagram of the system to be identified. Where x(t) is the known input profile and y(t) is the measured output profile and $h_{est}(t)$ is transfer function of the system to be estimated.

The transfer function of the system was estimated based on Fourier transforms of the input and output signals on the system.

$$H(\omega) = \frac{\overline{X(\omega)} \cdot Y(\omega)}{|X(\omega)|^2} = \frac{\hat{R}_{xy}}{\hat{R}_{xx}}$$

An inverse Fourier transform was then taken of the resulting transfer function. This data set was then cropped, limiting the memory of the system transfer function to a period of 10 samples or 2.5 hours. The known input data were then convolved with this transfer function to obtain the estimated cumulative system density response. These data were then analyzed to determine how well the predicted output matched the measured output. This resulted in an R^2 value of 0.912, confirming a good correlation between the model and the data.

Next, the derivative of the measured cumulative density data was taken. In order to obtain an accurate estimate of the derivative of the data, a first order least means squares fit was performed for each 4 samples of the data moving in a single sample step. The slope of this fit was then used as the representative value for the derivative of the data. These data were then analyzed using the same method as that of the cumulative density function data. This resulted in an R^2 value of 0.802, confirming that the predicted model correlated well with the estimated pulsatile drug delivery model as shown in Fig. 6.

The measured results show a time lag of around 45 minutes between the start of the therapy cycle and the detection of the $FeCl_2$ in the saline solution. This time lag is expected in the in-vitro studies due to the transport time required to traverse all the layers of the skin and reach the saline bath. In an in-vivo study this lag would be expected to be substantially smaller due to an active micro-capillary system just under the basal layer, obviating the need for passage of material through the dermis layer.

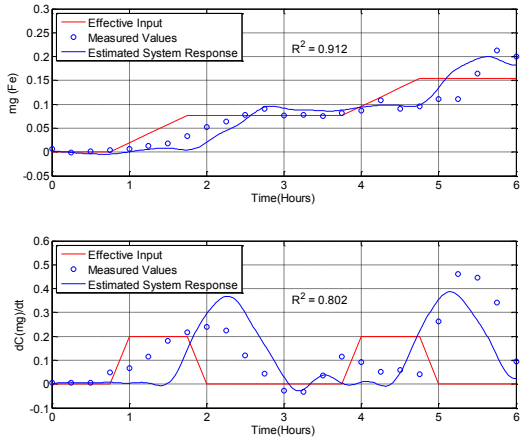

Fig. 6. Upper plot shows the cumulative input vs. the estimated system response based on an optimum cross-correlation FIR filter response of the measured system response. Lower plot shows the density input vs. the estimated system response based on an optimum cross-correlation FIR filter response of the measured system response.

IV. Discussion & Conclusion

In this study it was proposed that it would be possible to both actively drive a drug molecule through the layers of the skin during one phase of the current drive, as well as halt its passive diffusion during the opposite phase of the current drive. The results obtained agreed well with this premise, in that during times of therapy there was a net positive diffusion of the agent through the skin, while during the retarding phase the net flux of the agent approached zero.

However, a fairly large time lag existed between the onset of the therapy session and the detection of the agent. This lag was hypothesized to be an artifact of the in vitro experimental setup due to the lack of an active micro-capillary structure in the dermis layer of the skin. In an in vivo experiment an intact micro-capillary network could significantly shorten the detection time of the agent in the blood given that 93% (2.8 mm) [4] of the sample preps consisted of dead dermis tissue that the agent had to traverse prior to detection. As such, an active micro-capillary structure will likely reduce the time of detection by a factor of 15 (i.e., 3 minutes). This will need to be verified in vivo as literature indicates a time to half max of ~ 45 minutes for in vivo sumatriptan succinate (295.5 Daltons) [8].

The next steps would be to perform these experiments in vivo, as this should provide a much better estimate of the true time lag between the activation of the system and the detection of the agent in the bloodstream. This would also provide necessary data to refine the model to be able to predict how the system would react to a customized delivery profile.

In conclusion, a biphasic iontophoretic system was demonstrated, that has the potential to provide relief to patients whose conditions require an on-demand delivery of a therapeutic agent. This technology has the promise to overcome the limitations of current drug delivery technologies such as monophasic DC iontophoresis. We believe our system may result in improved patient care and management by providing rapid on-demand delivery without the adverse effects consequent to unwanted passive delivery during off-demand periods.

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