WIRELESS THERMAL MICRO-ABLATION OF SKIN FOR TRANSDERMAL DRUG DELIVERY

Jin-Woo Park[1], Jung-Hwan Park[1,2], Yong-Kyu Yoon[1], Yeun-Ho Joung[1], Seong-O Choi[1], Mark R. Prausnitz[2], and Mark G. Allen[1,2]
[1]School of Electrical and Computer Engineering, Georgia Institute of Technology, USA
[2]School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, USA.

ABSTRACT

This paper presents design, fabrication, and experimental results of a wireless induction heating system for generating micron-scale pores in the skin by thermal micro-ablation to dramatically increase skin permeability to drugs, while maintaining the patient-friendliness of conventional transdermal patches. The micro-heating element arrays have been fabricated using electrodeposition of nickel on a SU8 patterned structure. The heating element arrays have been characterized by applying wireless AC magnetic excitation using a coil, and applied to an *in-vitro* skin ablation experiment. The experiment has confirmed that fabricated micro-heating elements are able to generate heat sufficient to induce localized micro-ablation in human skin.

Keywords: Transdermal drug delivery, Induction heating, Micro-ablation

INTRODUCTION

Conventional drug delivery using pills or injection is often not suitable for new protein, DNA and other therapies [1]. An attractive alternative involves transdermal delivery from a patch [2], which avoids degradation in the gastrointestinal tract and first-pass effects of the liver associated with oral delivery as well as the pain and inconvenience of intravenous injection. Transdermal drug delivery also offers the possibility to continuously control the delivery rate, in contrast to conventional methods that deliver a large, discrete bolus. These advantages have led to a multi-billion dollar market for transdermal patches used for smoking cessation (nicotine), hormone replacement (estradiol), and other indications. Despite these advantages, transdermal drug delivery is severely limited by the poor permeability of human skin; most drugs do not cross skin at therapeutic rates and only a dozen drugs have been approved by FDA for transdermal delivery since the first patch was introduced 25 years ago. The skin's barrier properties come from the highly impermeable outer layer called stratum corneum, which is just 10 – 20 µm thick. Drugs that cross the stratum corneum barrier can generally diffuse to deeper capillaries for systemic distribution. For this reason, most approaches to increase transdermal delivery have emphasized disruption of stratum corneum microstructure using chemical [3] or physical [4] methods.

One approach to disrupting stratum corneum microstructure involves rapidly heating the skin surface to thermally ablate micron-sized regions of stratum corneum. If the thermal pulse is short enough, there is a steep thermal gradient across the stratum corneum, so that deeper viable tissues are not heated. In this way, the ablation is targeted to the stratum corneum so that living cells and nerves found deeper in the skin are not affected.

Previous approaches to thermal ablation of stratum corneum involved heating filaments [5] or an array of electrodes [6] to generate Joule heating by passing a short, high-current electric pulse. These device designs are all powered by means of wires physically connected to an external DC or RF power supply. These previous studies have reported the efficacy of the micro-ablation approach to increase skin permeability, but have the disadvantage that physical electrical connections are required to deliver the necessary energy from an external power source to the skin.

In this work, we present a wireless induction heating system for generating micron-scale pores in the skin by thermal micro-ablation that seeks to combine the efficacy of previous wired approaches with the improved convenience and likely higher patient compliance of wireless power delivery. The separation between the power source and the heating elements provides the potential for design flexibility, such as easier integration of ablation heating components with the drug patches and removal of the inconvenience of being 'plugged in' to an energy source, while maintaining the advantages of thermal micro-ablation.

DESIGN AND FABRICATION

Figure 1 shows a schematic diagram of the inductive heating system, including an AC power source, an excitation (induction) coil, and micro-heating elements. The induction heating is based on eddy current and hysteresis loss induced in the heating elements by the alternating magnetic field of the excitation coil [7]. In most metals, eddy current loss is the dominant source of induction heating. When a conductive material experiences alternating magnetic flux inside it, an electromotive force is induced in the material that causes a circulating current or eddy current, in accordance with Faraday's law of induction. This eddy current is converted into heat due to the Joule effect (i.e., resistive loss) in the heating material.

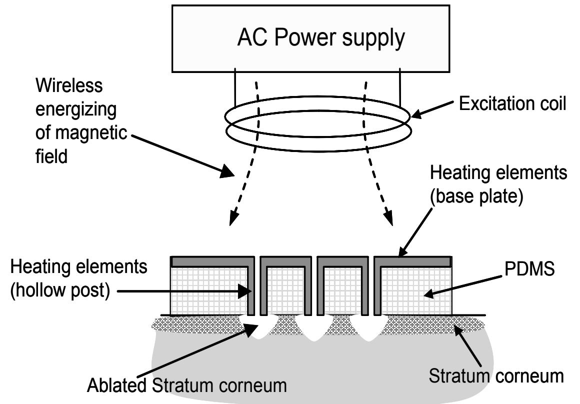
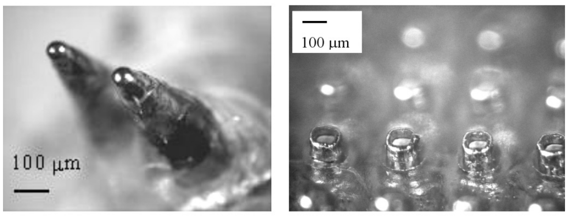


Figure 1. A schematic diagram of wireless inductive heating system for micro-ablation of stratum corneum.



(a) (b)

Figure 2. Photographs of microfabricated micro-heating elements: (a) Type A, two conical metal posts (tip diameter of 80µm, base diameter of 400µm, metal shell thickness of 50µm, and height of 2mm), (b) Type B, a section of an array of hollow metallic posts (inner tip diameter of 100µm, metal thickness of 30µm, post height of 400µm).

Two micro-heating element prototypes have been fabricated (shown in Figure 2): metallic cone structures (Type A) and a 20x20 array of hollow posts connected with a thin base plate (Type B). The fabrication process for the Type B is detailed in Figure 3. Photosensitive epoxy SU8 is patterned to form an array of posts on a dummy substrate (glass), and an electroplating seed layer of Ti/Cu is deposited on it (Figure 3a). Poly-methylmethacrylate (PMMA) is applied to the posts (Figure 3b). Reactive ion etching (RIE) is performed to expose the top portion of the posts, and the exposed seed layer is removed by wet-etching (Figure 3c). The remaining PMMA is removed by an organic solvent rinse. Nickel is electroplated on the seed layer, and the protruding SU8 is polished away (Figure 3d). Poly-dimethylsiloxane (PDMS) is applied evenly to the structure (Figure 3e). Again, RIE is performed to reveal the tip of the electroplated posts (Figure 3f). Finally, the total heating element is released from the dummy substrate (Figure 3g).

The Type B micro-heating element consists of two functional materials: Nickel and PDMS. Nickel was

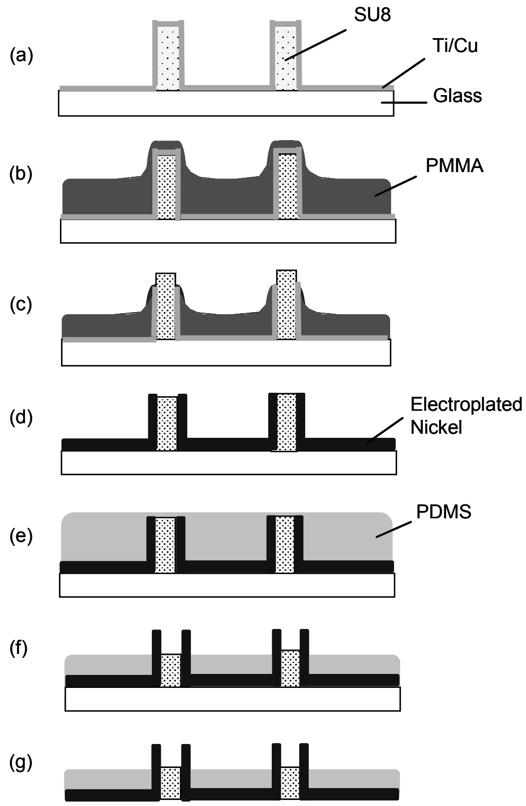


Figure 3. The fabrication process of the micro-heating element (Type B).

chosen as a heating material because it is nontoxic (although can be irritating to sensitized individuals) and has a high relative magnetic permeability that is favorable for induction heating. The heating material was structured to be a 20x20 array of hollow posts and a base plate. The base plate has two functions: one is to connect the array of hollow posts physically, and the other is to generate the induction (eddy current) heat and transfer to the hollow posts for rapid heating of the contacted skin. The PDMS layer is placed on top of the base plate to provide thermal insulation between the base plate and the skin. Therefore, in this design, only the end tip of the array of hollow posts and the PDMS layer will be contacted to the skin, and thermal ablation of skin would be localized to the shape of the post tip.

A solenoid type coil is chosen as a magnetic excitation coil, which fabricated by hand-winding 100 turns of magnet wire on an epoxy tube. The inner diameter of the coil is 1cm, and the coil length is 7mm.

EXPERIMENTAL RESULTS

The induction heating performance of the fabricated hollow post array (Type B) has been characterized while applying an AC magnetic field with the excitation coil. Liquid crystal polymer (LCP) paper, which changes its color permanently when a temperature exceeds pre-set

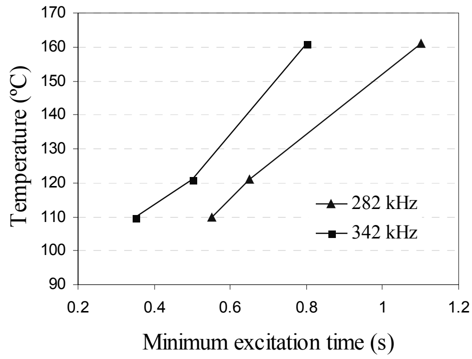


Figure 4. The induction heating characteristics of the hollow post array, type B (in Figure 2b)

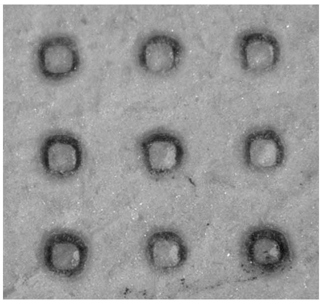


Figure 5. Photograph of the liquid crystal polymer paper (121ºC – temperature indicator) after applying induction heating of hollow metallic posts (in Figure 2b)

temperatures of 110, 121 or 161 ºC, was used as a temperature indicator for initial bench studies. The hollow post array was placed on top of the temperature-indicator papers inside the coil, and an AC current of controlled duration (0.05 second increment) and specified frequency was applied to the coil. The resulting temperature data is shown in Figure 4. The excitation time was recorded when each LCP paper changed color. Therefore, the x axis of graph represents the minimum time required to achieve the given temperature (the y axis). The RMS magnetic field applied to the heating element was approximately 50Gauss at frequencies of 282 and 342kHz. Since eddy current loss in the micro-heating element increases with applied frequency [8], the higher frequency excitation produced higher temperature than lower frequency as expected. Because the temperature needed for thermal ablation of skin is approximately 130°C [9], it can be concluded that the prototype hollow post array can successfully micro-ablate skin. Figure 5 shows an example of the temperature-indicating paper after excitation. The paper clearly indicates the localized heat pattern representative of the ring-shaped tip of the posts.

Finite element analysis (FEA) was performed to estimate induction heating power of the Type B heating element for the multiple frequencies, using ANSYS Emag 7.1. Three-dimensional simulation was performed for a quarter portion of the single post section, as shown in Figure 6. The simulation parameters and simulated results are given in Table 1. The result indicates that average power density (APD) of the 342kHz excitation is 1.4 times larger than that of 282kHz. Also, it is estimated that if the excitation frequency increases to 1MHz, the APD increases to almost 5.2 times that at 342kHz, which will provide a rapid temperature response of the heating element. The rapid heat response is expected to offer a steep thermal gradient across the stratum corneum, so that any unnecessary heat effect to the viable skin could be minimized. The simulated induction power density for the cross-section of heating element at 342kHz is shown in Figure 7. Figure 7 indicates that non-uniform heating power generation due

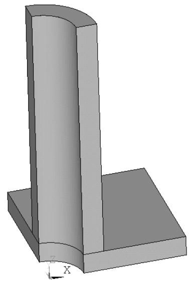


Figure 6. Geometry for 3D simulation of induction heating (an angled view)

Table 1. The simulation parameters used and results

Relative permeability of Ni	100
Electrical resistivity of Ni (Ω·m)	0.69×10^{-7}
Average power density at 282 kHz (W/m^3)	0.37×10^9
Average power density at 342 kHz (W/m^3)	0.52×10^9
Average power density at 1MHz (W/m^3)	2.7×10^9

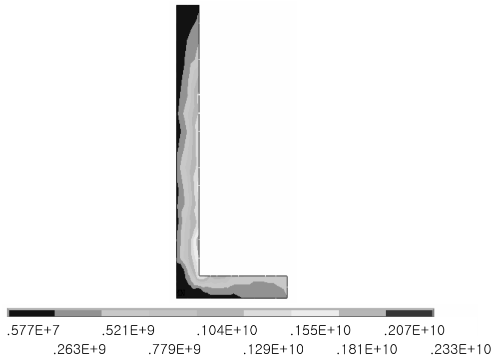


Figure 7. A simulation plot showing induction heating power density at 342kHz (a cross-sectional view, W/m^3)

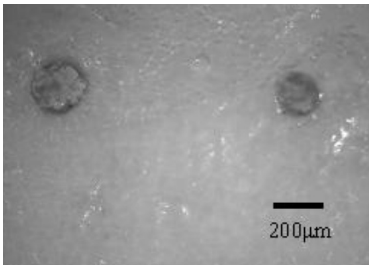
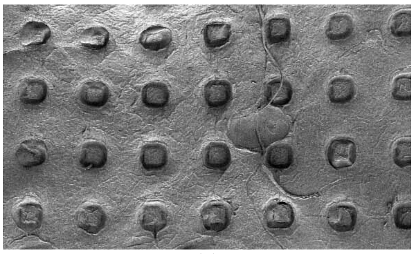
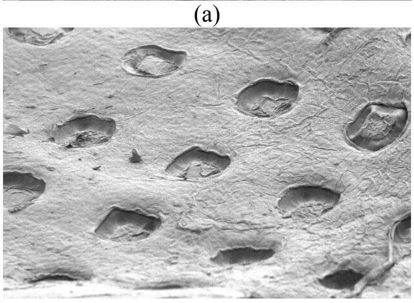


Figure 8. Photomicrograph of thermally ablated human cadaver skin using the metallic cone structures, Type A (in Figure 2a)



(a)



(b)

Figure 9. SEM of thermally ablated human cadaver skin using the hollow posts array, Type B (in Figure 2b): (a) a top view, and (b) an angled view

to the non-uniform eddy current distribution for the given geometry is present: the outer perimeter of the post generates more power than the inner perimeter.

The micro-heating elements were applied to an *in-vitro* skin ablation experiment. Figure 8 shows a photomicrograph and Figure 9 shows a scanning electron micrograph (SEM) of human cadaver skin (stratum corneum and epidermis) after the micro-heating elements were activated and removed. Two sites of local skin micro-ablation in the position of the conical tips (Type A), and an array of donut-shaped openings in the shape of the tips of the hollow posts (Type B) are shown in Figures 8 and 9, respectively. These pictures indicate that fabricated micro-heating elements are able to generate localized micro-ablation in human skin.

In order to simulate an *in-vivo* experiment, the Type A heating element was applied and energized on the skin of a hairless rat immediately after death. The skin

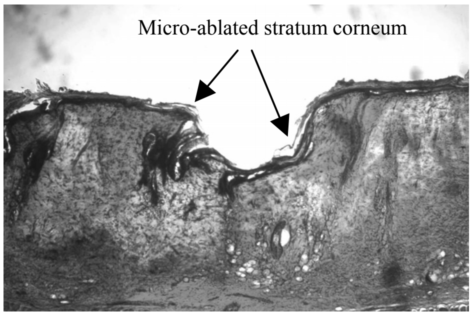


Figure 10. Photomicrograph of a histological section of a rat skin after thermal micro-ablation

specimen was then removed and prepared for sectioning using a cryostat microtome. As shown in Figure 10, the skin was indented due to pressing the needle-shaped heating element against the skin, and apparently the stratum corneum has been ablated along the surface of the dent.

CONCLUSIONS

A wireless induction heating system for transdermal drug delivery has been demonstrated. The system was designed to increase drug permeability of skin by thermal micro-ablation. Wireless functionality for generating localized heating has been confirmed by experiment. *In-vitro* experiments have been performed to micro-ablate skin, and showed that the developed system can generate micron-scale pore on the skin. The quantitative experiment for measuring drug delivery efficiency of generated pores is on-going work.

REFERENCES

[1] R. Langer, “Drug delivery and targeting,” *Nature*, 1998, 392, pp.5-10.

[2] M. R. Prausnitz, S. Mitragotri and R. Langer, “Current status and future potential of transdermal drug delivery,” *Nat Rev Drug Discov*, 2004, 3, pp. 115-124.

[3] E.W. Smith and H.I. Maibach, *Percutaneous Penetration Enhancers*, CRC Press: Boca Raton, FL, 1995.

[4] A. Naika, Y. N. Kalia, and R. H. Guy, “Transdermal drug delivery: overcoming the skin barrier function,” *PSTT* 3: 318-326 (2000).

[5] J. Bramson, K. Dayball, C. Evelegh, Y. H. Wan, D. Page, and A. Smith, "Enabling topical immunization via microporation: a novel method for pain-free and needle-free delivery of adenovirus-based vaccines," *Gene Ther*, 2003, 10: 251-260

[6] A. Zohar, “Transdermal drug delivery and analyte extraction,” 2004, U.S Patent No. 6,711,435.

[7] S. Zinn and S.L. Semiatin, *Elements of Induction Heating*, Electric Power Research Institute, Palo Alto, CA, 1988.

[8] J. Lammeraner, and M. Stafl, *Eddy current*. London: Iliffe Books Ltd., 1966, Chapter 2.

[9] J. A. Eppstein, M. R. Hatch, and D. Yang, “Microporation of human skin for drug delivery and monitoring applications,” 2000, U.S Patent No. 6,142,939.