Original Article

Development of a portable iontophoretic drug delivery device with in-vitro experiments for androgeneticalopecia treatment

Qun Wei[1], Zia Mohy-Udin[2], Jin Ho Cho[3]

ABSTRACT

Objectives: This study presents the development of a portable drug delivery device using an iontophoresis method to treat the androgenetic alopecia with in-vitro experiment. To treat this condition, the drugs for alopecia treatment need to be delivered into the scalp. Therefore, iontophoretic stimulation was used in a portable drug delivery device to enhance the penetration of the drug delivery.

Methodology: The designed device consisted of a drug container, an iontophoretic stimulation part and a rechargeable part. The iontophoretic part included a voltage boosted circuit, a protection circuit to achieve the iontophoresis effect and to protect the device. The device was tested with an oscilloscope and an in-vitro experiment was also performed to test the operation of the device.

Results: According to the experiment's results, the iontophoresis circuit board performed well as did the designed drug delivery device. And the results of the in-vitro experiment also performed well with the penetration enhanced drug delivery via stimulation with the iontophoresis method.

Conclusion: The presented portable iontophoretic device enhances the penetration of the drug delivery as proven by the experiment. Also, a positive feature of the device is that it allows patients to use it everywhere by themselves. Improving the device's functionality and usage safety will be researched in the future.

KEYWORDS: Iontophoresis, Drug delivery device, In-vitro experiment, Penetration.

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INTRODUCTION

Alopecia, sometimes results in baldness. A health condition called alopecia areata in which hair is lost from some or all areas of the body, usually from the scalp.[1,2] If untreated, or if the disease does not respond to treatment, complete baldness can result in the affected area, known as alopecia totalis. There are many reasons as to what could cause alopecia to occur: such as chemical breakage from overuse, frequent use of chemical relaxers, or chronic exposure to traction on the hair such as Traction alopecia, etc. Recently, many hair loss therapeutic treatments have been invented,[3,4] such as oral medicine, liniment, self-hair transplant, mesotherapy, etc. Among these methods, medication is the most widely used treatment for alopecia. Patients can daub liquid medicine onto their affected areas by themselves.

There is a drug for treating the non-scarring, generalized alopecia effectively developed by M. H. Kwack, S. H. Shin and etc. [5]In order to improve the drug delivery of using this drug and make it easy to be used in everywhere, a portable drug delivery device using an iontophoresis method for androgenetic (non-scarring, generalized) alopecia treatment is proposed. Iontophoresis is a technique using a small electric charge to deliver a drug through the skin. It is basically an injection with-out a needle.[6-8]Theiontophoresis provides a mechanism that enhances the penetration of hydrophilic and charged molecules across the scalp.[9]

For the iontophoretic stimulation circuit that includes a rechargeable part, a Lithium Manganese Dioxide rechargeable battery was used. It was fixed on a small sphericity liquid drug container which can be held by one hand. The opening of the drug container was designed as a rolling ball structure to control the flux of the drug. Furthermore, the rolling ball was made of metal material and connected to an electrode of the output of the iontophroetic stimulation circuit that was set up in the inside of the drug container. Four cathode electrodes from the iontophoretic circuit were placed around the drug container. When patients hold the bottle with their hand and touch the rolling ball opening to the affected part of their scalp, the drug will be delivered via the rolling ball and will penetrate the scalp by iontophoresis effect. The iontophoretic stimulation circuit was tested by oscilloscope in order to study its performance. And the proposed portable iontrophoretic drug delivery device was assembled,and an in-vitro experiment was used in this experiment to prove its performance. The device performed well in improving the penetration of the drug delivery by iontophoresis method.

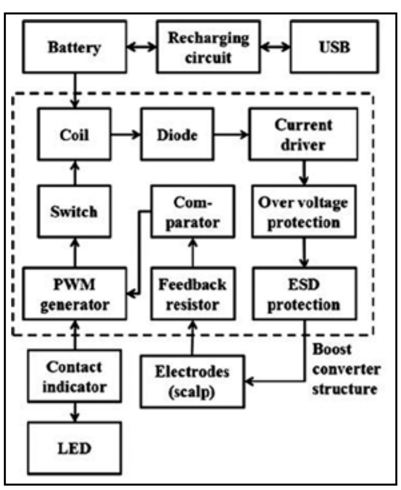


Fig.1: Block diagram of designed iontoporetic circuit.

METHODOLOGY

Iontophoretic stimulation circuit design: The iontophoretic stimulation circuit was de-signed to include two parts: the stimulation circuit and the power supply. The block diagram of the designed iontophoretic circuit is shown in Fig.1. As noted in a previous research, a pulsed wave-form supposedly allows the skin to depolarize and return to its initial state before the onset of the next pulse.[10] A PWM (Pulse Width Modulation) generator was designed in this circuit for making the pulse signal. Also the PWM generator is operated as a switch controller.[11] It is a method of controlling the amount of power to a load without having to dissipate any power in the load driver. The amount of power delivered to the load is proportional to the percentage of time that the load is switched on.

When the switch turns on, the current from the battery will be permitted to through the boost convert that includes coil, diode and current driver. Through the boost converter, the output voltage will be greater than its input DC voltage. Since the miniaturized electronic device is sensitive to over voltage, and silicide diffusions increase the surface heating in MOS devices under ESD (electrostatic discharge) conditions,[12,13] an over voltage and an ESD protection system were incorporated into the designed circuits to protect the components. Finally, the output current for the iontophoretic stimulation will be delivered to the affected part when patient touch the device to their scalp.

For the power supply, a Lithium Manganese Dioxide rechargeable battery was chosen to power the drug delivery system, because it is very small and light making it portability, and the rechargeable circuit was designed to connect to a mini Universal Serial Bus (USB) to recharge the battery easily.

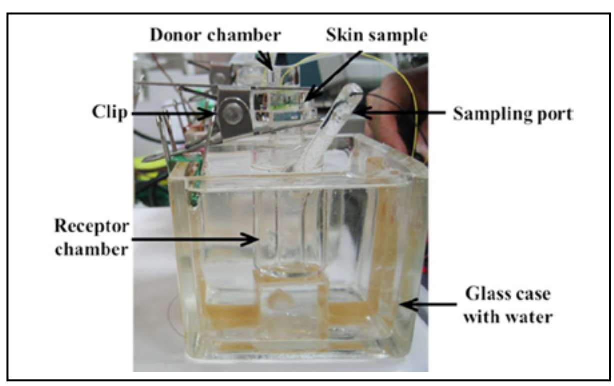


Fig.2: The Franz cell is using in the in-vivo experiment.

Design of the electrodes: The top of the drug container was designed as a rolling ball structure to control the flux of the drug. Also the rolling Balls are used as the output electrode to attach the scalp,sothe rolling ball was coated with Ag-cl. In addition, four ground electrodes that connected with the iontohporetic circuit ground are placed around the drug container and they were also coated with Ag-cl. The iontophoretic stimulation will start when the patient puts the opening to his affected part. The current from the device will go through the body and return to the device when his hand touches the ground electrodes.

Experiments: Franz Cell, a standard glass diffusion cell for in vitro penetration studies, is shown in Fig.2. This design has the advantage of having easy temperature control of the water beneath the skin.[14] The in-vitro experiment was designed to analyze three statements of drug delivery with iontophoretic stimulation; normal state without stimulation, stimulation with negative current, and stimulation with a positive ion.[15] The object skin was taken from the back of a hairless female mouse with its subcutaneous fat removed.[16] It was put on the top of the receptor chamber and its wrinkles were smoothed out.[17] It was covered with the donor chamber, the skin was laid between the receptor chamber and the donor chamber, and the leak of the skin was checked.

The receptor chamber was filled with 1X6 ml phosphate buffered saline (PBS) while the donor chamber was filled with 0.004 M 0.5 ml L-Ascorbic acid 2-phosphate sesquimagnesium salt hydrate water-soluble vitamin (Ap-Mg) and covered with a lid to keep the Ap-Mg from evaporating. As Fig.3 shows three Franz cells were stabilized to at temperature of 37 degree with a stirrer whose speed was 400 PRM by a multi-plate (Barnstead Super-Nuova) for an hour. Then, two Franz cells were stimulated by the portable iontophoretic drug delivery device for an hour. One of the Franz cell's receptor chambers was inserted into the electrode of the iontorphretic circuit ground and the skin was connected with the out-put electrode to stimulate it with a negative ion.

Another one was stimulated by the same iontophoretic device, but the two electrodes were put in opposite positions than the previously discussed one for positive ion stimulation. The portable iontophoretic drug delivery device was supported with a 2.6V input voltage constantly. After one hour of stimulation, all the solution in the Franz cells' receptor chamber was sampled from the sampling port every twenty minutes for an hour. During sampling, the PBS of all the receptor chambers was filled up with the same amount as the sampled solution. The samples were analyzed by high performance liquid chromatography to get the experiment's results.

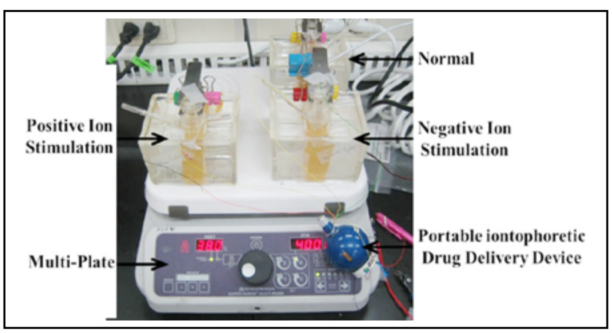


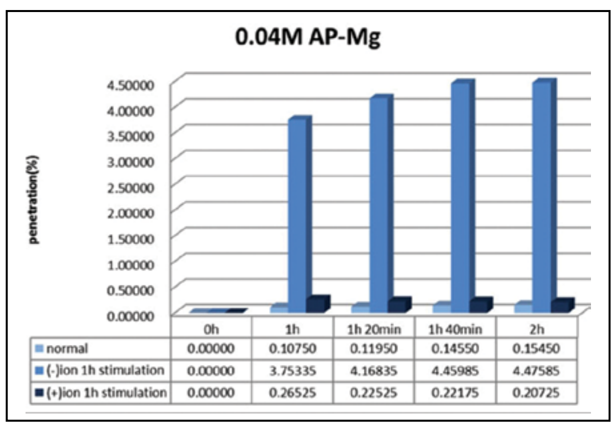
Fig.3: The 3 statements of drug delivery analysis with iontophoretic stimulation by the proposed portable iontophoretic drug delivery device on multi-plate.

RESULTS

From the in-vitro experiment of three states, the value of the AP-mg that penetrated the skin from donor chamber to the receptor chamber is shown in Fig.4, it shows the percentages of penetration of AP-mg in the in-vitro experiment with three statements. The penetration of the normal state and the negative ion stimulation increased as time increased. The negative ion stimulation penetration was 40 times bigger than the other statements. In this in-vitro experiment, that tested the iontophroteic drug delivery device, portable the negative ion stimulation had the best results.

DISCUSSION

As the results of the experiments show, the portable drug delivery device using iontophoresis



	0h	1h	1h 20min	1h 40min	2h
normal	0.00000	0.10750	0.11950	0.14550	0.15450
(-)ion 1h stimulation	0.00000	3.75335	4.16835	4.45985	4.47585
(+)ion 1h stimulation	0.00000	0.26525	0.22525	0.22175	0.20725

Fig.4:Shows the sampled solution's percentages of 0.04 AP-Mg that penetrate the 3 same skin samples with different stimulation with portable iontophroesis device for an hour.

method for alopecia treatment performed well in terms of the electrical system and in-vitro experiments. The proposed iontophoretic system was able to achieve the electrical iontophoretic stimulation with a pulse signal. The overvoltage protection can protect the circuit up till 15V. And the ESD protection was able to achieve IEC 61000-4-2. The assembled portable iontophoretic drug delivery device is able to be used by one hand easily everywhere. The negative ion stimulation with the proposed device performed the best in the in-vitro experiment of the three statements.

The AP-mg penetration was enhanced greatly by stimulating it with the negative ion. And the AP-mg penetration with negative ion stimulation is larger than those of the other two statements by about 30 times. The positive stimulation result shows the penetration of the AP-mg was only larger than the normal state by about two times. Furthermore, the penetration decreased as time in-creased. This phenomenon was assumed to be due to the neutralization reaction that happened as a result of the reaction of the stimulated positive ion with the AP-mg solution; the AP-mg solution was presented in negativeion.[14]

The proposed portable drug delivery device was used in androgenetic alopecia. In the future works, the device will be developed to treat the female-pattern baldness. And, the pulse signal of the iontophoretic stimulation will be researched. Adjusting the duty cycle and the frequency of the current can get the optimum results. And, the current can be delivered under different waveforms, such as sinusoidal, square, triangular and trapezoidal.[9] Also the rechargeable circuit will be improved, since the voltage of the USB power supply is 5V and rechargeable battery voltage is 3V, a regulator circuit is need to be designed in the circuit to decrease the USB voltage to 3V. In addition, the safety of using the proposed portable iontophretic drug delivery device will be studied in in-vivo experiment.

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REFERENCE

1. Richard BO, William DJ, Timothy B. Andrew's diseases of the skin: Clinical Dermatology. 9th ed. Philadelphia: Saunders; 2000.
2. Draelos ZD.Alopecia Areata, 2007.Available from: http://MedicineNet.com.
3. Ihm CW. Treatment of alopecia areata. Korean J Dermatol.2005;10:1309-1315.
4. Kim BJ. Research for using medical machine to treat the alopecia.Korean J Dermatol.2010;20:92-93.
5. Kwack MH, Shin SH, Kim SR, Im SU, Han IS, Kim MK, et al. L-Ascorbic acid 2-phosphate promotes elongation of hair shafts via the secretion of insulin-like growth factor-1 from dermal papilla cells through phosphatidylinositol 3-kinase. British J Dermatol. 2009;160:1157-1162.
6. Merino V, Lopez A, Hochstrasser D.Noninvasive sampling of phenylalanine by reverseiontophoresis.J Controlled Release.1999;61:65-69.
7. Numajiri S, Sugibayashi K, Morimoto Y.Non-investigateinvasive sampling of lactic acid ions byiontophoresis using chloride ion in the body as an internal standard.J Pharmaceutical and Biomedical Analysis.1993;11:903-909.
8. Hwa EJ. Transdermal drug delivery system.JKorean Industrial and Chemistry Engineering. 2005;16:15-20.
9. Yogeshvar NK, Aarti N, James G, Richard HG.Iontophoretic drug delivery.Advanced Drug Delivery Reviews. 2004;5:619-658.
10. Ajay KB. Electrically assisted transdermal and topical drug delivery. London: Taylor and Francis e-Library; 2003.
11. Grahame H, Thomas AL. Pulse width modulation for power converters: principles and practice. Wiley-IEEE Press; 2003.
12. Duvvury C, Diaz C. Dynamic gate coupling of NMOS for efficient output ESD protection. Reliability Physics Symposium.1992;141-150.
13. Mark S. Drug delivery engineering principles for drug therapy. USA: OxfordUniversity Press; 2001.
14. Skerrow D, Skerrow CJ. Methods in skin research.John Wiley and Sons Ltd; 1985.
15. Burnette RR, Marrero D. Comparison between the iontohphoretic and passive transport of TRH across exised nude mouse skin. J Pharm Sci. 1986;75:738-743.
16. Hwang IY. Enhanced iontophoreticdelivery of risedronate Sodium across hairless mice Skin. J Korean Pharm Sci.2010;2:79-84.
17. Shin DS. Iontophoretic Delivery of Prostaglandin E1. J Korean Pharm Sci.1999;2:111-115.

Authors Contribution:

QW conceived, designed and manufactured system and manuscript writing.

ZMU did data collection and review the manuscript.

JHC did review and final approval of manuscript.

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