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Transparent microprobe array fabricated by MEMS hot embossing technology for photodynamic therapy application

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Abstract: This work describes a novel transparent micro-needle array for photodynamic therapy (PDT) applications. This micro-needle array, with 250 um in height and 35 um in diameter, was placed onto skin and penetrated the cuticle yet not reaching the corium layer, so as to avoid pain and bleeding but achieve superior light transmission efficiency. For PDT applications, this design can significantly reduce the required incident power and therefore avoid additional damage to surrounding healthy tissue. Practical in-vivo test on human skin demonstrates the improved power transmission efficiency (PTE) of two types of needle arrays is 1.41 and 1.71 times better than the condition without using micro-needle array.

Keywords: MEMS, photodynamic therapy, needle array, hot embossing

Classification: Micro- or nano-electromechanical systems

References

[1] X. Sun and W. N. Leung, "Photodynamic therapy with pyropheophorbide-a methyl ester in human lung carcinoma cancer cell: efficacy, localization and apoptosis," *Photochem Photobiol*, vol. 75, no. 6, pp. 644–651, Feb. 2002.

[2] D. Goldberg, "Photodynamic therapy in skin rejuvenation," *Clinics in Dermatology*, vol. 26, no. 6, pp. 608–613, Nov. 2008.

[3] M. R. Hamblin, D. A. O'Donnell, N. Murthy, C. H. Contag, and T. Hasan, "Rapid Control of wound infections by targeted photodynamic therapy monitored by in vivo bioluminescence imaging," *Photochem Photobiol*, vol. 75, no. 1, pp. 51–57, Feb. 2002.

[4] J. Tardivo, A. Del Giglio, C. de Oliveira, D. Gabrielli, H. Junqueira, D. Tada, D. Severino, R. de Fàtima Turchiello, and M. Baptista, "Methylene blue in photodynamic therapy: From basic mechanisms to clinical applications," *Photodiagnosis and Photodynamic Therapy*, vol. 2, no. 3, pp. 175–191, 2002.

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[5] D. J. Granville and D. W. C. Hunt, "Porphyrin-mediated photosensitization0-taking the apoptosis fast lane," *Current Opinion in Drug Discovery and Development*, vol. 3, no. 2, pp. 232–243, 2000.
[6] B. Y. Kogan, "Nonlinear photodynamic therapy. Photochemical dose levelling within a tumor by saturating a photosensitizer's triplet states," *Photochem. Photobiol. Sci.*, vol. 3, no. 4, pp. 360–365, Feb. 2004.
[7] H. J. G. E. Gardeniers, R. Luttg, E. J. W. Berenschot, M. J. de Boer, S. Y. Yeshurun, M. Hefetz, R. van't Oever, and A. van den Berg, "Silicon micromachined hollow microneedles for transdermal liquid transport," *J. Microelectromechanical Syst.*, vol. 12, no. 6, pp. 855–862, Dec. 2003.
[8] C. L. Chang, C. W. Chang, C. M. Hsu, and J. C. Chiou, "Power-efficient wireless sensor for physiological signal acquisition," *J. Micro/Nanolith., MEMS MOEMS*, vol. 8, no. 2, 02110, June 2009.
[9] M. Shimada, Y. Yamada, M. Itoh, and T. Yatagai, "Melanin and blood concentration in a human skin model studied by multiple regression analysis: assessment by Monte Carlo simulation," *Phys. Med. Biol.*, vol. 46, no. 9, pp. 2397–2406, Sept. 2001.
[10] J. B. Dawson, D. J. Barker, D. J. Ellis, E. Grassam, J. A. Cotterill, G. W. Fisher, and J. W. Feather, "A theoretical and experimental study of light absorption and scattering by in vivo skin," *Phys. Med. Biol.*, vol. 25, no. 4, pp. 695–709, 1980.

1 Introduction

Photodynamic therapy (PDT) is administered to treat malignant tumors [1], various skin disorders [2], wound infections [3], and other diseases, as well as for cosmetic purposes in skin rejuvenation [2]. Treatment involves a photosensitizing agent, in which a visible light is irradiated to either terminate cancerous cells or cure precancerous cells instead of surgery [4]. Efficacy of PDT heavily relies on the photosensitizing agent, light, and oxygen. Physicians medicate patients and apply the photosensitizing agent on the affect part of the patient body and, then, illuminate the affected parts of a patients' body with various wavelengths of light, depending on the disease. When the photosensitizing agent is treated by light with a special wavelength, a reactive oxygen species is produced, subsequently damaging bio molecules and terminating cells [5]. Although this noninvasive and painless therapy distinguishes itself from traditional surgery, the non-uniform spatial distribution of the photochemical dose is a major limitation [6]. Tissues of the human body vary in light absorption, subsequently incurring a non-uniform light dose when irradiating the treated spot upon the affected part of skin. Additionally, the layers of skin located close to a light source receive too high of a photochemical dose, negatively affecting the human body [6].

MEMS-based micro-needle array has received consideration in biomedical applications recently, especially in drug delivery [7] and physiological signal sensing. In micro drug delivery system, drug is injected through hollow needle structure into patient's tissue. The microstructure design allows the needle array pricked onto patient's skin without uncomfortable feeling. In physio-

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logical signal sensing system, micro needle array provides lower impedance and enhance the sensing system performance [8]. In this paper, we present an alternative application in optical biomedical engineering by using transparent micro-needle array. Additionally, the needle array in previous works may be manufactured with deep reactive ion beam etching, thick-film lithography and electroforming techniques for the shafts and tips; however, traditional all-silicon fabrication methods in previous works are prohibitively expensive.

This study describes a relatively low cost and easy fabrication method, which combined two-phase process for disposable transparent micro-needle array manufacture. Note that the expensive ICP process was used only one time for the first silicon needle mold. Then, hot-embossing technique was applied to duplicate the first needle mold into transparent micro-needle arrays. The material of duplicated micro-needle array can be polyimide (PI) or polymethylmethacrylate (PMMA), which has better light propagation capability than glass and very low cost than silicon. The carefully designed transparent micro-needle array can avoid pain and bleeding but achieves superior light transmission efficiency. For photodynamic therapy applications, this design can significantly reduce the required irradiation power and therefore avoid additional damage to surrounding healthy tissue.

Practical *in-vivo* light transmission experiment with two different density needle array designs demonstrates the improved power transmission efficiency (PTE) of the two types of arrays is 1.41 and 1.71 times better than the condition without using micro-needle array.

2 Concept

Human skin structure is a layered composition, can be simplified as the outer skin layer, stratum corneum (SC), stratum germinativum (SG), and the dermis layer, as shown in Fig 1 (a). The stratum corneum is constantly renewing itself and consists of dead cells. The scattering coefficient of the epidermis is approximately half that of the dermis [9]. When treatment involves light irradiating with wavelength λ , such as a low power laser on the human skin, the skin reflects, scatters and absorbs the light simultaneously. Each layer of skin layer differs from light absorption. The propagation result of the incident light depends on the absorption of the skin. Also, when a specified intensity of received light power is required in PDT applications, high scattering and reflection could result in not only high power consumption but also extra damage to the other tissue surrounding the curing target. The Lambert–Beer law offers a simplified model of light propagation in the human skin (Fig 1 (a)). When an incident light with interrogating energy $\boldsymbol{I_0}$ illuminates into the human skin, the relationship between incident light power $\boldsymbol{I_0}$ and the attenuated light power $\boldsymbol{I}$ can be expressed as [10]:

$$I(L) = I_0 10^{-aLC}$$

Where $\boldsymbol{L}$ represents the penetrating depth of light in the human skin, $\boldsymbol{a}$ denotes the equivalent absorption coefficient of all skin, and $\boldsymbol{C}$ denotes the

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concentration of the absorbing substance. Denotes that the total area of needle array chip is $\boldsymbol{A}$, and the total area of transparent micro-needle is $\boldsymbol{A'}$, when the proposed needle array is placed onto skin and penetrated though the SC layer into SG layer, as shown in Fig. 1 (b), the penetrating depth of light is reduced from $\boldsymbol{L}$ to $\boldsymbol{L'}$. And the total attenuated light $\boldsymbol{I}$' can be express as:

$$I' = \left(1 - \frac{A'}{A}\right) I_0 10^{-aLC} + \frac{A'}{A} I_0 10^{-a'L'C'} \tag{1}$$

Where $\boldsymbol{a'}$ denotes the equivalent absorption coefficient of SG layer and dermis, and $\boldsymbol{C'}$ denotes equivalent concentration of the absorbing substance of the SG layer and dermis. In the area of micro needle array, most of the incident light can be transferred into SG layer through the needle shaft, thus, the reflection and absorption of SC and SG layer could be reduced. Therefore, by using the proposed transparent needle array as the light-guide, the required target depth with required light power intensity could be achieved by lower interrogating energy.

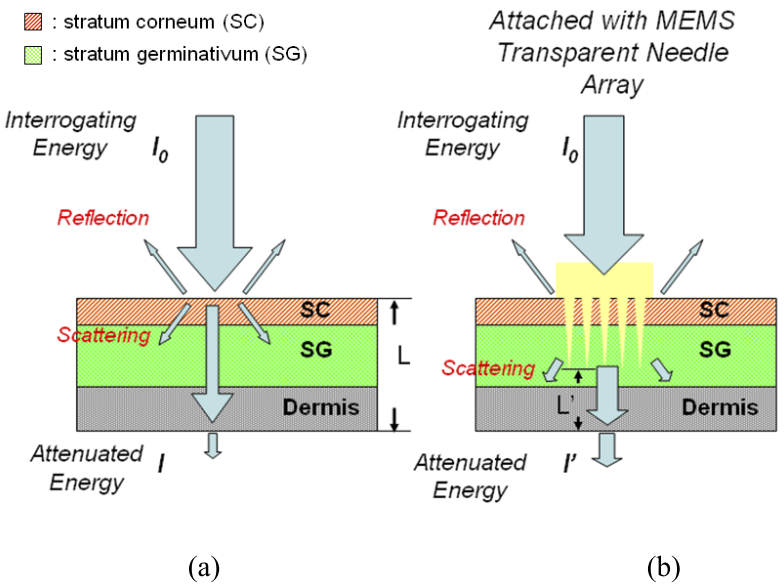

Fig. 1. The model of light propagation in human with (a) direct illumination, and (b) illumination through penetrate micro needle array.

3 Fabrication process of micro-needle array

For medical applications, micro-needle array is usually defined as disposable device for healthy and safety reasons, and low fabrication cost becomes one of the important requirements to achieve disposability for disposability objective. In this paper, a relatively low cost and easy fabrication method, which combined ICP etching and hot embossing approaches, is presented for micro-needle array manufacture. Compare to previous works, the expensive deep silicon etching process was used only one time for the first needle mold.

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Then, hot-embossing technique was applied to duplicate the first needle mold into transparent micro-needle arrays. Note that duplication process could be repeated at least 120 times with guaranteed hot-embossing result.

The fabrication flow can be separated into two phase: first is the fabrication of silicon needle array mold, and the second is the repeated-and-repeated duplication process using hot-embossing technique. Fig. 2 (a) illustrates the first fabrication phase: First, Cr was defined for etching hard mask. Then, a two-step ICP process was introduced to perform isotropic and anisotropic etching for the shaft tip and 250 um–height shaft, respectively. Finally, the hard mask was stripped by wet etching.

Next, the second fabrication phase is shown in Fig. 2 (b) and described as follows: First, polydimethylsiloxane (PDMS) was selected and spun onto Si substrate as the molding layer with curing at 90°C. Then, the silicon mold fabricated in the first fabrication phase was pressed into PDMS to form the second mold with hole-array. After well-controlled temperature recipe, the silicon array mold was removed from the PDMS mold. Notably, base on the well-controlled stated parameters including curing time and temperature, the

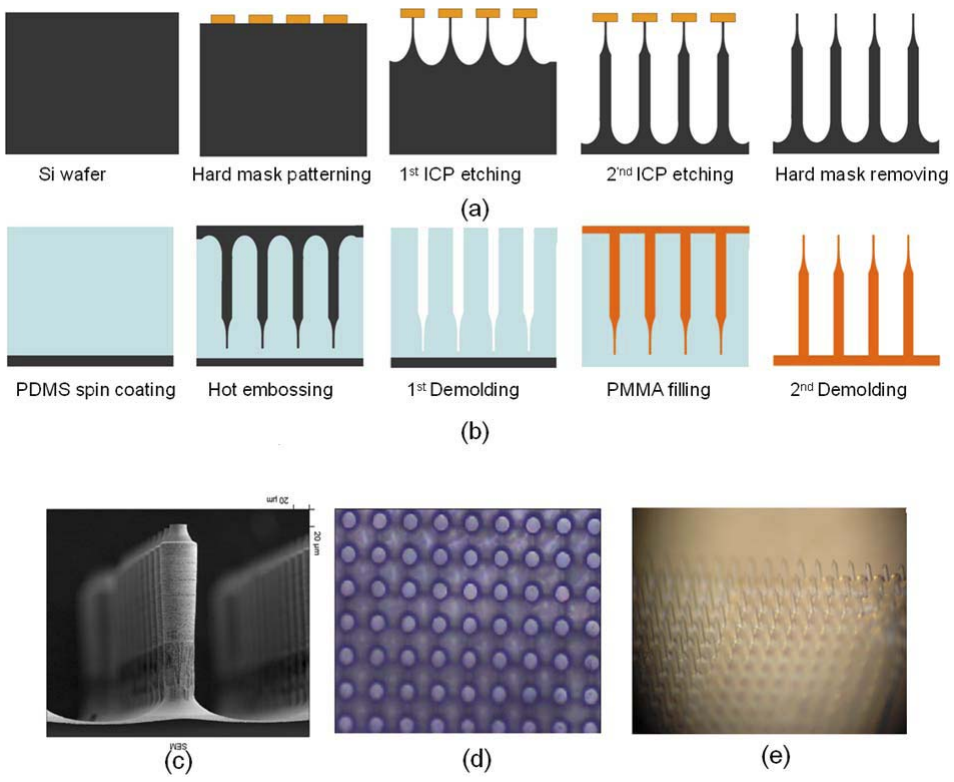

Fig. 2. The fabrication process and photos of and micro needle array. (a) The pre-process to manufacture Si based mold of micro needle array (b) The hot embossing process to manufacture transparent polymer needle array. (c) SEM picture of Si based mold of micro needle array. (d) The PDMS needle-hole mold. (e) The optical microscope photograph of transparent micro needle array.

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released process is relatively easy without using any additional execution such as O_2 plasma treatment which is used in previous works. And then, polymer material PMMA was injected into the PDMS mold to form the transparent needle array. Finally, the successfully performed transparent needle array was released from the PDMS mold and diced for further experiments. Fig. 2 (c)-(e) shows the photographs and SEM results of the transparent micro-needle array.

4 Experimental result and discussion

Fig. 3 (a) shows the light transmission experiment setup, which demonstrates the enhanced light transmission efficiency when using transparent needle arrays as light transmitting media. In this experiment, light source includes a 660 nm-wavelength laser diode and focusing lens was mounted onto finger with 3 cm distance between finger and lens. The emitter power is adjusted by a current controller. Below the finger, a light receiver that can receive and measure the transmitted light power was well fitted to the backside of

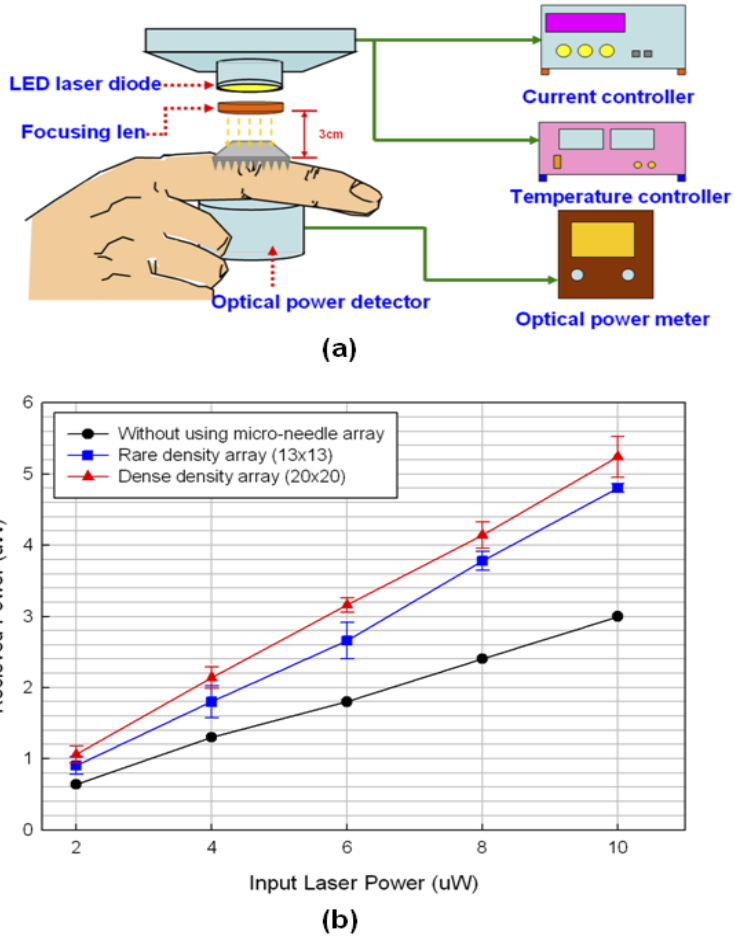

Fig. 3. The illustration of (a) light transmission experiment setup and (b) experiment results of input light intensity versus output light intensity via micro-needle arrays with different density.

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the finger. All experiments are performed in a dark room to eliminate the influence of excess light. To confirm the relationship between the needle array density and light transmission rate, two needle arrays with the same size 4 mm × 4 mm × 0.3 mm, but different array density (needle number : 20 × 20 and 13 × 13) are prepared for test. Each needle array was tested under the parameter of input laser power from 2 mW to 10 mW with an interval of 2 mW.

Fig. 3 (b) summarized the measurement results, where the black, blue and red lines indicate the received light power via skin, skin with rare-density array and skin with dense-density array, respectively. The results reveals shows that under the same LED power, the transparent micro-needle array can significantly enhance the propagation efficiency. According to the experimental result, the improved PTE of dense density needle array and rare needle array are 41% and 71% times better than the condition without using micro-needle array.

Note that the laser spot size on the array is about 3.5 mm in diameter. In the same spotted area, the difference of received power between rare and dense density arrays comes from the different area ratio of needle part. Consider the PTE result of the rare-density array in Fig. 3, the area proportion of the needle part and non-needle part in the spotted area, the calculated PTE of needle part is 25 times larger than the flat part of array. By applied this result back into the calculation of the PTE of dense-density array, the calculated PTE of dense-density array is about 1.89 times better than the condition without using micro-needle array, which is very close to our measured result (1.71).

5 Conclusion

This work presents an alternative application in optical biomedical engineering by using transparent micro-needle array. The two-phase fabrication flow combined ICP etching and hot embossing approaches, is presented for micro-needle array manufacture and achieving low cost batch fabrication. The hot-embossing-based micro-needle array, with 250 um in height and 35 um in diameter, was placed onto skin and penetrated the cuticle but not reaching the corium layer, so as to avoid pain and bleeding but achieve superior light transmission efficiency. For photodynamic therapy applications, this design can significantly reduce the required incident power and therefore avoid additional damage to surrounding healthy tissue. Practical in-vivo light transmission experiment with two different density array designs demonstrates the improved transmitted power of dense density needle array and rare needle array are 1.41 and 1.71 times better than the condition without using micro-needle array.

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