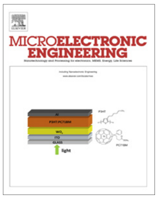
Microelectronic Engineering 128 (2014) 12–18

Contents lists available at ScienceDirect

Microelectronic Engineering

journal homepage: www.elsevier.com/locate/mee



Fabrication and characterization of gold coated hollow silicon microneedle array for drug delivery

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ARTICLE INFO

Article history:
Received 8 April 2014
Received in revised form 12 May 2014
Accepted 31 May 2014
Available online 10 June 2014

Keywords:
Microneedles
Dry etching
Sputtering
Electroplating

ABSTRACT

In this paper, we present the fabrication and characterization of Ti and Au coated hollow silicon microneedles for transdermal drug delivery applications. The hollow silicon microneedles are fabricated using isotropic etching followed by anisotropic etching to obtain a tapered tip. Silicon microneedle of 300 μm in height, with 130 μm outer diameter and 110 μm inner diameter at the tip followed by 80 μm inner diameter and 160 μm outer diameter at the base have been fabricated. In order to improve the biocompatibility of microneedles, the fabricated microneedles were coated with Ti (500 nm) by sputtering technique followed by gold coating using electroplating. A breaking force of 225 N was obtained for the fabricated microneedles, which is 10 times higher than the skin resistive force. Hence, fabricated microneedles can easily be inserted inside the skin without breakage. The fluid flow through the microneedles was studied for different inlet pressures. A minimum inlet pressure of 0.66 kPa was required to achieve a flow rate of 50 μl in 2 s with de-ionized water as a fluid medium.

1. Introduction

Oral drug administration is commonly employed by the physicians for treating diseases like diabetes, etc. However, oral drug administration is not always feasible due to poor drug absorption through gastrointestinal tract. Transdermal drug delivery technology has emerged as the most common approach to overcome this disadvantage [1,2]. Furthermore, transdermal drug delivery technology has many advantages such as, a specific skin area can be targeted. Also, dose reduction and precise control over volume of drug can be achieved. In addition, use of microneedles in transdermal drug delivery system causes less pain which helps in treating patients having needle phobia.

Out of plane microneedles have tremendous applications in drug delivery system and body fluid extraction [3]. Geometrical constraints on these microneedles are imposed by the physiology of human skin. Fig. 1 shows the cross section of human skin together with microneedles array. The outer most layer of the human skin is known as stratum corneum (20–30 μm thick). The next layer is epidermis with a thickness of 100 μm [4,5]. For painless epidermal drug delivery, it is desirable that the microneedle has to penetrate to a depth of 150–200 μm within the skin. These requirements impose constraint on the length of the microneedle to be in the range of 150–200 μm. Previously, in order to reduce the insertion force and hence to avoid the possible needle damage while inserting into the tissues, as well as the possible needle blockage, different shapes of silicon (Si) microneedles have been reported in the literature. Table 1 gives an overview of the reported typical dimensions of the hollow Si microneedles fabricated till date. Griss et al. and Gardenier et al. have demonstrated the sharp tip microneedles with side openings. However, the disadvantage with the side opened microneedle is, opening is too far from the needle tip. Thus, the needles need to be inserted much deeper into the tissue to avoid drug leakage. Khanna et al. reported the microneedle having opening in the tip. But, in their approach the tapering of microneedles tip was achieved by gradual reduction of the photoresist method, which involves multiple steps [6].

One of the most important requirements for microneedles is the material biocompatibility with skin and the drugs. Technologies have been established to realize biocompatible microneedles using various materials including metals and polymers [7]. However, Si is not well established as a biocompatible material for implantable bio-devices unlike well studied materials like titanium, stainless steel and gold [8]. Processing of polymer, metal and stainless steel for micro fabrication still needs extensive research for mass production. Hence we have explored the possibility of taking advantage of well established Si technology for fabricating microneedle

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http://dx.doi.org/10.1016/j.mee.2014.05.039
0167-9317/

Table 1
Typical properties of the hollow out-of plane Si microneedles.

Reference typical dimensions (μm)	Khanna et al. [6]	Griss et al. [19]	Gardenier et al. [9]	Stoeber et al. [4]	Ashraf et al. [10]	Jurčíček et al. [11]
Inner diameter	118.8	60	70	40	60	10–25
Outer diameter (tip)	119.8	10	0	50	–	–
Outer diameter (base)	165	160	250	425	150	–
Length	200	250	350	200	250	100–120

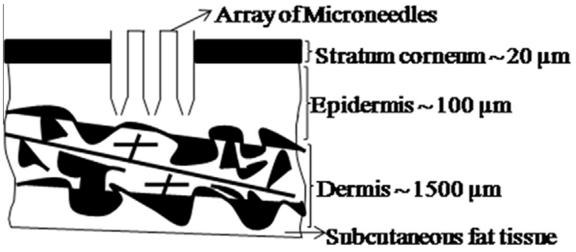

Fig. 1. Cross-section of human skin.

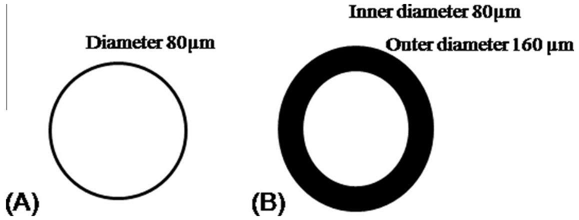

Fig. 2. Mask design for hollow Si microneedles. (A) Back side mask for inner lumen. (B) Front side mask for inner lumen and needle walls.

with minimum process steps and coating them with biocompatible material to make it a cost effective biocompatible device for drug delivery.

In this paper, we present the design and fabrication of tapered hollow out of plane Si microneedle by single step isotropic and anisotropic process using Deep Reactive Ion Etching (DRIE). The fabricated microneedles were coated with titanium (Ti) by sputtering and gold (Au) by electroplating method to make it suitable for implantable bio-devices. The mechanical failure of the microneedles was experimented using suitable in-house built experimental setup. Fluid flow through the array of microneedles was studied for different inlet pressures.

2. Experimental

2.1. Fabrication of flat tip microneedles

In this work, we have employed two-step lithography process for the realization of microneedles. Fig.2 shows the mask structures used to fabricate microneedles and Fig. 3 shows the graphical illustration of steps involved for fabrication. Initially, a double side polished four inch Si wafer was cleaned in piranha solution for 15 min. The cleaned wafer was oxidized using thermal oxidation furnace (dry-wet-dry oxidation) and this creates a SiO_2 layer (about 1 μm) on both sides of Si wafer. The SiO_2 thickness is confirmed by ellipsometer (step1 in Fig. 3). Photolithography was carried out from backside to etch the inner bore of Si wafer using a mask structure shown in Fig. 2A. The patterned SiO_2 on the backside of the Si wafer is etched by Reactive Ion Etching (RIE) as shown in step 2 of Fig. 3. This process is followed by DRIE to etch Si from backside for a depth of 160 μm and is shown in step 3 of Fig. 3 (using Bosch process, 15 μm min^{-1} is employed). In the next step, photolithography was carried out from front side of the wafer to etch Si using a mask structure shown in Fig. 2B. The patterned SiO_2 on the front side of the Si wafer is etched by RIE is shown in step 4 of Fig. 3. The mask is designed to etch both hole and pillar structures using a single mask as shown in step 5 of Fig. 3. Therefore, SiO_2 is left only on top of the microneedle wall region. Using RIE process, the SiO_2 on top of the microneedle wall is removed to get Si microneedles. Finally, an array of hollow Si microneedles having a height 300 μm was obtained with 80 μm inner and 160 μm outer diameter~~s~~ as shown in Fig. 4.

2.2. Fabrication of tapered tip microneedles

Si microneedles fabricated using the above mentioned process does not have tapered tip to facilitate easy penetration into the skin. It is a known fact that, microneedles without tapered end require more force to penetrate into the skin [6]. Therefore, we have fabricated microneedles with tapered tip using isotropic etching process (15 μm/min undercut and 15 μm/min deep etch recipe is used). Subsequent to step 4 indicated in Fig. 3, one minute isotropic etching (as shown in step A of Fig. 5) has been carried out which is followed by anisotropic etching to achieve a tapered tip with top oxide layer (as shown in step B of Fig. 5). In order to obtain tapered tip, the top oxide on the microneedle~~s~~ is removed using RIE process which is schematically shown in step C of Fig. 5. Fig. 6B shows the fabricated tapered tip microneedle with oxide layer on the top. The top oxide layer on the microneedle tip was removed using RIE process (shown in step A of Fig. 4). Finally, an array of hollow tapered Si microneedles of height 300 μm was obtained with 130 μm outer diameter and 110 μm inner diameters at the tip.

2.3. Metal coating on microneedles

Further, Si microneedles are coated with Ti and Au to make them suitable for implantable bio-device. A seed layer of Ti metal of thickness 500 nm was coated on Si microneedles using sputtering method as shown in Fig. 7. The conductive seed layer is necessary for electroplating of Au. Therefore, 1 μm thick Au was deposited on the Ti coated Si microneedles. After coating Ti and Au on microneedles, the through hole of the microneedle was confirmed by using an optical microscope (with the illuminating light) as shown in the Fig. 8. Microneedle insertion and liquid flow was studied by connecting microneedle substrate to a 6 mm silicone tube using PolyDiMethylSiloxane (PDMS) as shown in Fig. 9. Ti deposition on inside as well as outside of the needle wall was examined by making a vertical cross sectional cut (shown in Fig. 10A) using Focused Ion Beam (FIB) technique. The presence of Ti layer confirmed using Energy Dispersive X-ray technique (EDAX) is shown in Fig. 10.

2.4. Mechanical strength and adhesion

An experiment was carried out in order to estimate the breaking force of the microneedles. The schematic of the experimental setup used is shown in Fig. 11. It essentially consists of a solid aluminum rod, microneedle array, aluminum supporting plates and a load cell. In order to measure the breaking force for microneedles, the axial load is applied on the microneedles using a load cell. The load cell is made to move slowly towards the microneedle array at a speed of 2.5 μm ms^{-1}, and the measured microneedle breaking