Feasibility of Micro Electrode Array (MEA) Based on Silicone-Polyimide Hybrid for Retina Prosthesis

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ABSTRACT

Purpose: To adopt micropatterning technology in manufacturing silicone elastomer-based microelectrode arrays for retinal stimulation, a silicone-polyimide hybrid microelectrode array was proposed and tested *in vivo*.

Methods: Gold microelectrodes were created by semiconductor manufacturing technology based on polyimide, and were hybridized with silicone elastomer by spin coating. The stability of the hybrid between the two materials was flex and blister tested. The feasibility of the hybrid electrode was evaluated in rabbit eye by reviewing optical coherence tomography (OCT) findings after suprachoroidal implantation.

Results: The flex test showed no dehiscence between the two materials for 24 h of alternative flexion and extension from -45.0° to +45.0°. During the blister test, delamination was observed at 8.33±1.36 psi of pressure stress; however, this property was improved to 11.50±1.04 psi by oxygen plasma treatment before hybridization. OCT examination revealed that, the implanted electrodes were safely located in the suprachoroidal space during the 4-week follow-up period.

Conclusion: The silicone-polyimide hybrid microelectrode array showed moderate physical properties, which are suitable for *in vivo* application. Appropriate pretreatment before hybridization improved electrode stability. *In vivo* testing indicated that this
electrode is suitable as a stimulation electrode in artificial retina.

**Key words:** silicone elastomer, polyimide, hybrid electrode, artificial retina
INTRODUCTION

In electrical retinal prostheses for the blind, polyimide, parylene, silicone elastomer, and other biocompatible materials are used as the base material for the stimulation electrode array. Silicone elastomer is a well-known biomaterial used in various medical applications, including filler in plastic surgery and coating material for cochlear implants and deep brain stimulators [1-3]. The flexibility and softness of silicone elastomer can minimize scarring from unintended damage during implantation and its durability is sufficient to protect an implanted prosthetic device for more than 20 years. However, fabrication of neural prostheses using silicone elastomer mainly depends on a manual process because the material’s softness and non-planar surface are not suitable for conventional semiconductor manufacturing technologies. As device design has become more delicate and complex, manual fabrication has become more difficult, and the volume of the silicone-coated devices have increased, which can increase manufacturing cost and risk of implantation failure [4, 5].

The polyimide-based microelectrode array (MEA) was developed based on silicon microfabrication technology and had shown moderately good results [6-13]. Although this technique can provide highly reliable and low-cost MEA manufacturing, the stiff
edges of a thin film structure may induce unwanted scratches during insertion and
movement of the arrays into the target position. Moreover, film thickness needs to be
kept below several tenths of a micrometer for low stress insertion into a fragile retina,
and often, an additional insertion guide needs to be prepared to support the implantation
procedure.

Aiming to synergistically combine the suitability of the silicone elastomer for
implantation and the micro fabrication technology of the polyimide for high density
array integration, this study describes a silicone-polyimide hybrid MEA for use in
neural prostheses.
MATERIALS AND METHODS

Fabrication of silicone-polyimide hybrid MEA

The fabrication process of the silicone-polyimide hybrid MEA is shown in Fig. 1. A 1-µm thick Silicon oxide was deposited on a Si wafer by plasma-enhanced chemical vapor deposition (PECVD) as a sacrificial layer to be used for releasing the structure in buffered hydrofluoric acid (BHF). A 10-µm thick lower polyimide (PI2525; HD Microsystems, Parlin, NJ, U.S.A.) layer was coated on the Si wafer and cured on a hot plate. Three layers of titanium, gold, and titanium (500Å, 4000 Å, and 1000 Å, respectively) were evaporated in that order on the lower polyimide layer with an E-gun (ZZS550-2/D; Maestech, Korea). Photolithography was used to make stimulation electrode sites, external connection pads, and create conduction lines between them. The upper titanium layer (1000 Å) was used as an etch mask during the site and pad opening process, and the lower titanium layer was used as an inter-layer for conducting gold adhesion on the polyimide. After patterning of the metal layers, a 6-µm thick upper polyimide layer was added under stress-free conditions. An additional 1000 Å titanium layer was evaporated on top of this upper polyimide layer to be used as an etch-stop mask to define the MEA outline. The whole structure was defined and sites and pads
were opened using reactive ion etching (RIE). The polyimide MEA structure was released using buffered hydrofluoride solution (NH$_4$F: HF = 7:1). Typically the etch process for releasing the structure took only a few seconds so the top titanium metal layer exposed to the etch solution during this time was able to protect the underlying gold electrode layer. The etch stop was detected by observing the color of the composite metallic layers changing from metallic silver to yellowish gold, which represented the thickness reduction of the titanium overlayer.

The released polyimide MEA structure was then mounted on a photoresist-coated Si wafer and became firmly attached through photoresist curing. For improved hybridization of the polyimide and silicone elastomer, oxygen plasma treatment was applied using RIE for 3 min under 0.1 Torr pressure at 100 watts of power with 100 sccm (cm$^3$ min$^{-1}$) of oxygen inflow. Oxygen plasma in an RIE process is known to change a hydrophobic polyimide surface of the polyimide to a hydrophilic one, which may enhance the adhesion of the silicone elastomer to the polyimide surface by chemical bonds formed from surplus bonding chains [14, 15]. Then the polyimide MEA was dehydrated on a hotplate at 120°C for 3 min.

The silicone elastomer (MED-4211; Nusil Technology, Carpinteria, CA, USA) was coated onto the pre-treated surface of the polyimide MEA by spin coating. The spin
speed was increased gradually from 0 to 4,000 rpm for 120 sec, and kept at 4,000 rpm for additional 30 sec. This resulted in a deposited silicone elastomer layer with approximately 64-µm thickness on the polyimide MEA and the overall thickness of the silicone-polyimide hybrid MEA became approximately 80 µm.

The silicone-coated wafer was kept in a vacuum chamber for 30 min to flatten the curved silicone surface generated by spinning and to eliminate any remaining air bubbles in the silicone elastomer. Final curing was done on a 120°C hot plate for 30 min. The sample was then kept at room temperature for 24 h. The final structure was meticulously defined by a precise manual cutting of the silicone layer along the polyimide edge. By soaking the wafer in acetone to dissolve the adhesive photoresist, each electrode was released, and the residues were cleaned up by methanol and distilled water.

**Flex and Blister tests with silicone-polyimide hybrid MEA**

The silicone-polyimide hybrid MEA was tested *in vitro* and *in vivo*. A flex test was used to verify stable adhesion between the silicone elastomer and the polyimide. The MEA was secured at either end by one fixed clip and one mobile clip. The mobile clip was connected to the servo-motor controlled by computer software (Fig. 2(a) and (b)),
and was alternatively flexed and extended 28800 times from -45.0° to +45.0° over 24 h.

The cross-sectional view of the tested MEA was carefully inspected using optical microscopy and field emission scanning electron microscopy (FESEM) in order to verify the adhesion state between the polyimide and silicone layers. Three samples were inspected before and after the flex test.

A blister test [16, 17] was performed to evaluate the effect of pre-treatment on the polyimide surface before silicone coating. Through a 2 mm ø hole, positive pressure was applied with CO₂ gas to the sample mounted in the test frame. By increasing gas pressure with a precision pressure controller (Harris Products Group, Mason, OH USA), the stability of the hybridization between the silicone elastomer and the polyimide was measured quantitatively, see Fig. 2(c) and (d). In this test, the adherence force between the two layers was defined as the pressure at which the silicone-polyimide hybrid started to be split. During testing, 15 electrode arrays were divided into 3 groups according to the pre-treatment methods. The groups were MEA without pre-treatment, MEA with RIE treatment only, and MEA with RIE and dehydration before silicone coating. Five electrodes were allocated to each group.
Implantation of silicone-polyimide hybrid MEA in rabbit eye

In vivo experiments were performed with New Zealand White rabbit weighing 2.0−2.5 kg. The Association for Research in Vision and Ophthalmology (ARVO) Statement on the Use of Animals in Ophthalmic and Vision Research was followed during all procedures. Surgical implantation of the MEA was performed under general anesthesia achieved by repetitive intramuscular injection of 25 mg of ketamine and 6 mg of xylazine per kg of body weight. After conjunctival incision by limbal approach, the internal part of the MEA was inserted into the suprachoroidal space through the scleral tunnel at the 12 o’clock site, 5 mm from the corneal limbus. The external part of the MEA was fixed onto the external surface of the sclera with 8-0 Vicryl® (Ethicon Inc, Somerville, NJ, USA) suture and biocompatible acrylate glue (Histoacryl®, B. Braun Medical, Bethlehem, PA, USA). All procedures were performed carefully under the fundus through examination with a wide field lens. After implantation of the MEA, the conjunctiva was repaired as previously described [18].

Optical coherence tomography (Cirrus OCT, Carl Zeiss, Dublin, CA, U.S.A.) [19] was used to observe the biocompatibility and biostability of the implanted MEA. Fundus photographs were taken on the day of surgery, as well as 1, 2, and 4 weeks after implantation, and any changes in the retina and MEA were noted.
RESULTS

The Silicone-polyimide hybrid MEA was successfully manufactured by the described methods (Fig. 3(a)). Suprachoroidal implantation of the MEA was successfully done (Fig. 3(b)) without significant complications such as suprachoroidal hemorrhage or retinal damage throughout all surgical procedures.

Flex tests showed good adhesion between the silicone and polyimide layers without any evidence of splitting (Fig. 3(c) and (d)). On blister tests, delamination was observed at 8.33 ± 1.36 psi in samples without pretreatment before silicone coating (Fig. 4). Samples with dehydration only before silicone coating showed delamination at 9.00 ± 1.41 psi, while samples with oxygen plasma pretreatment only at 11.50 ± 1.04 psi and samples with both oxygen plasma treatment and dehydration at 11.80 ± 1.72 psi, i.e. at significantly higher pressures than those with no oxygen plasma treatment (p< 0.01, t-test). This indicates that oxygen plasma treatment can enhance the stability of the hybridization between silicone and polyimide.

During the 4 week follow-up period, the implanted MEA was safely located without any damage to the operation site or the electrode. This was verified by OCT examination (Fig. 5). Although there was a minute fluid collection in the suprachoroidal
space along the inserted MEA immediately after the operation, this fluid was completely
absorbed during follow-up. There were no definite postsurgical complications during
the follow-up period.
DISCUSSION

Even though silicone elastomer show good biocompatibility and durability in various medical applications, it is difficult to integrate them into the microfabrication process because of their susceptibility to the high temperatures commonly used in silicon microfabrication technology. A cured silicone elastomer may be denatured if exposed to heat over 260°C [20], but the curing temperature of polyimide may be 300°C or higher [21]. For this reason, silicone elastomer handling should be separated from the polyimide manufacturing steps. Another point is that patterning of a silicone elastomer is almost impossible using conventional microfabrication technology as there is no proper agent for wet-etching of silicone elastomer. In case of dry-etching of silicone elastomer by oxygen plasma, the metallic or photoresist mask on the silicone layer is required. The metallic mask causes the silicone surface to wrinkle through the sudden drop of the wafer surface temperature immediately after the metallization. The photoresist mask is usually not suitable because it cannot tolerate the long dry-etching time for the patterning of the thick silicone elastomer layer. Thus, a two-step approach for the fabrication of the silicone-polyimide hybrid MEA was proposed and successfully carried out in this study. Furthermore, because silicone elastomer is a highly viscous
material, the spin speed was elevated, but controlled below 4000 rpm to avoid a bumpy final surface formation.

Surface treatment of the polyimide layer with oxygen plasma showed enhanced adhesion between the polyimide and the silicone layers. Although surface dehydration may help improve adhesion by increasing the opportunity for chemical bonding between the layers [22], no statistical benefit was detected in this study. An implanted MEA would be soaked in body fluids with an abundance of salts and ions in long-term in vivo applications, thus long-term stability of the structure and biocompatibility with surrounding tissues should be tested in future experiments.

Polyimide or other kinds of film-based structures show highly flexible characteristics on stress orthogonal to the film surface, but have stiff and sharp edges. This flexibility will make electrode manipulation difficult, and the sharp edge can induce damages to the retina or choroids during the implantation surgery if the target subretinal or suprachoroidal spaces were not formed before insertion. Thus a guide is usually needed during implantation of flexible electrode arrays; also, the edge of the film electrode should be polished or rounded. Although high flexibility can also be controlled by increasing film thickness, it also increases postoperative complications related to stiffness. Silicone elastomer-based polyimide MEAs may simultaneously solve these
problems. Soft and rounded edges can reduce damage to the retina and choroids during the surgery and the enhanced recoiling force provided by the silicone elastomer layer make implantation much easier and more convenient, eliminating the need for a guide during surgery.

We show here that microfabrication technology can be useful in developing a MEA composed of two or more materials with different properties. Such a microfabrication technique may contribute to the creation of low-cost silicone MEAs for reliable neural prosthetics in the future.
CONCLUSION

A novel combination of silicone elastomer and polyimide was used to produce a biocompatible MEA for use in artificial retina. A stepwise approach was established to overcome the heat-labile property of the silicone elastomer layer. Both flex and blister tests showed satisfactory stability and durability of the hybrid MEA. RIE and oxygen plasma dehydration of the polyimide surface enhanced adhesion to the silicone elastomer. In-vivo epiretinal and subretinal implantations were successfully performed without damage to the MEA or adjacent tissues in rabbit eye.

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FIGURE LEGENDS

Figure 1. Schematic illustration of the silicone-polyimide hybrid electrode fabrication process.

Figure 2. Feasibility test setups for the hybrid MEA structure: (a) Flex test setup to measure adhesion of the MEA during and after implantation and (b) its schematic diagram. (c) Blister-test setup to evaluate the effect of pretreatment of the polyimide surface before silicone coating and (d) its schematic diagram.

Figure 3. Result of the silicone-polyimide hybrid MEA fabrication process and feasibility tests of the structure: (a) Microscopic MEA structure from frontal (upper) and cross-sectional (lower) views; (b) Suprachoroidal implantation of hybrid MEA structure into a rabbit eye. (c) Sectional view of MEA structure before flex test and (d) after flex test. (Magnification: 13192×, field emission scanning electron microscopy)

Figure 4. Result of blister test for adhesion properties between polyimide and silicone elastomer according to pretreatment of the polyimide surface before silicone coating. (a)
Control group (8.33±1.36 psi) (b) Dehydration (9.00±1.41 psi) (c) O₂ plasma treatment (11.5±1.04 psi) (d) O₂ plasma treatment and dehydration (11.8±1.72 psi).

Means and STD bars are shown (n=5)

Figure 5. Immediate and weekly postoperative optical coherent tomographic findings of a rabbit retina and a suprachoroidally implanted microelectrode array.
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