Title

Study on Elemental Technologies for Creation of Healthcare Chip Fabricated on Polyethylene Terephthalate Plate

Author(s)

OKI, Akio; TAKAMURA, Yuzuru; FUKASAWA, Takayuki; OGAWA, Hiroki; ITO, Yoshitaka; ICHIKI, Takanori; HORI, Yasuhiro

Citation

IEICE TRANSACTIONS on Electronics, E84-C(12): 1801-1806

Issue Date

2001-12-01

Type

Journal Article

URL

http://hdl.handle.net/10119/4727

Rights


Description

None
Study on Elemental Technologies for Creation of Healthcare Chip Fabricated on Polyethylene Terephthalate Plate

Akio OKI†, Yuzuru TAKAMURA†, Takayuki FUKASAWA†, Hiroki OGAWA†, Yoshitaka ITO††, Takanori ICHIKI†††, and Yasuhiro HORIIKE†, Nonmembers

SUMMARY Elemental technologies have been studied to establish the healthcare chip which is an intelligent micro analytical system to detect human health markers from a trail of blood. A two steps process for deep quartz dry-etching was discussed in order to overcome the issues of concave-shaped defects at the bottom of grooves. A coating with 2-methacryloyloxyethylphosphorylcholine (MPC) polymer was studied to suppress the adsorption of bio-substance onto the inner wall of the flow channel on chip and good bio-compatibility was achieved for suppression of protein adsorption and blood cell adhesion. A prototype of healthcare chip was fabricated on polyethylene terephthalate (PET) plate using a micro molding technique. Using this chip, the ion concentrations of pH, Na⁺, K⁺, Ca²⁺ were successfully measured with embedded ion sensitive field effect transistors (ISFET's).

key words: health checking, microcapillary, electrosmosis, MPC polymer, ISFET

1. Introduction

To protect our health from environmental problems such as global warming and the hormone-mimicking synthetic chemicals, we are now studying a healthcare device which checks our daily health as an application of µ-TAS (micro-Total Analytical System) [1]. As shown in the illustration of Fig. 1, the final structure of the device will be such a blood analytical system embedded on a Si integrated circuit (IC), which involves chemical sensors, data acquisition and correction circuits, operation sequencer, communication means, and so on. This chip can be applicable for virtual health diagnostics at any demanded locations, by being installed to a handy phone, which will be a most popular mobile terminal of the highly developed information culture in future. To establish our goal, we have started to develop an analytical chip, in which a trace amount of blood is injected into a microcapillary by a pumping method, and typical health markers such as pH, O₂ and CO₂, Na⁺, K⁺ and Ca²⁺ cations, uric acid, lactic acid and glucose can be measured using various chemical sensors. However, we have to solve many issues as shown in Fig. 1; (1) a painless needle collecting blood of nano litter, (2) fabrication techniques of a microcapillary in quartz or polymer plate (3) a biocompatible capillary which allows the flow blood without clogging or denaturalization, (4) a transport means of the serum into a capillary, and (5) embedded chemical sensors to detect the health markers.

As pioneering work, an integrated chemical analysis system of O₂, CO₂ and pH in blood was developed using a micro-flow cell [2]. However, no attention was paid for the bio-compatibility in this work. Ishihara et al. have noted the coating effect of 2-methacryloyloxyethylphosphorylcholine (MPC) polymer [3] on quartz surface. The MPC polymer makes surfaces similar to natural bio-membranes, so that the surfaces can interact in a compatible manner with biocomponents such as proteins and cells. This polymer has been utilized for many applications, for instance, artificial blood vessels, coatings on soft contact lenses, catheters and top coatings of various in-vivo sensors. We have already reported electrosmosis injection of blood serum into the MPC polymer coated microcapillary fabricated on quartz plate [4].

This paper reports on elemental technologies of a micro blood analytical system made on PET (polyethylene terephthalate) plate, focusing on (1) fabrication process employing dry etching technologies, (2) the bio-

Fig. 1 Illustration of a final structure of healthcare device and the issues to be developed.
compatibility of the capillary whose inner wall is coated with the MPC polymer, and (3) measurement of health makers of pH and concentrations of Na\(^+\), K\(^+\) and Ca\(^{++}\) employing an ISFET (ion sensitive field effect transistor) embedded in the plate.

2. Fabrication Process of Microcapillary PET Chip and Experimental

Figure 2 shows a fabrication process of a microcapillary made by PET. At first, a reversal microcapillary pattern with 30 \(\mu\)m \(\times\) 30 \(\mu\)m cross-sections was fabricated on a quartz plate with 2 cm \(\times\) 2 cm area. A Cr film with a 1.5 \(\mu\)m thickness masked by a resist (ZEP 7000; Nihon Zeon) delineated by EB (electron beam) lithography was etched by Cl\(_2\)ICP (inductively coupled plasma) at 10 mTorr at the 18 cm downstream region from the antenna, where the etch rate selectivity of the Cr film to the EB resist was improved \([5]\). Using this Cr mask, the microcapillary patterns were dry-etched employing a planar type NLD (neutral loop discharge) \([6]\) with a C\(_3\)F\(_8\) + 70% CF\(_4\) mixture. The etching pressure was 3 mTorr. The 13.56 MHz power added to the antenna was 800 W. The gas of C\(_3\)F\(_8\) alone was chosen because it was one of the substituting gases for global warming. When the plasma with C\(_3\)F\(_8\) alone was employed during quartz etching, we suffered from not only wider pattern width than original one, but generation of numerous concave-shaped defects on the bottom surface of the quartz plate. These issues are discussed in detail at the following section. The fabricated quartz plate with the reversal capillary pattern in this way was pressed onto a PET plate by a pressure of 1.5 MPa and at a temperature of 90\(^\circ\)C for 10 minutes. Figure 3 shows an embossed microcapillary pattern on the PET plate. Next, two ISFET chips made by the Shindengen Kogyo Corporation were embedded on another PET plate by hot press in the same condition as the previous molding. Holes for reservoirs and wastes, in which electrodes should be inserted to apply high voltage, were drilled in the PET. Finally, the microcapillary-pattern molded PET plate was bonded to the ISFET’s embedded PET plate in the condition of 0.7 MPa and 100\(^\circ\)C. The finished PET chip was demonstrated in an inset photograph in Fig. 2.

The present ISFET device included two transistors in a chip. The gate materials were Ta\(_2\)O\(_5\) on Si\(_3\)N\(_4\) fabricated by CVD (chemical vapor deposition) on thermally grown SiO\(_2\). The sensing area was 10 \(\mu\)m long \(\times\) 360 \(\mu\)m wide. The Ta\(_2\)O\(_5\) was used for the ion sensitive substance for the pH measurement in this paper.

For the measurement of the Na\(^+\), K\(^+\), and Ca\(^{++}\) cation concentrations, a mixture of 100 mg polyvinylchloride (PVC), 3 ml tetrahydrofuran (THF), 10 mg bis[(12-crown-4)methyl]-2 dodecyl-2-methylmalonate, 102 mg 2-nitrophenyldodecyl ether (NPOE) and 1 mg tetrakis (4-chlorophenyl) borate potassium salt (K-TCPB), a mixture of 100 mg PVC, 3 ml THF, 10 mg bis[benzo-15-crown-5]-4-methylpimelate, 102 mg NPOE and 1 mg K-TCPB, and a mixture of 100 mg PVC, 3 ml THF, 10 mg 4,16-Bis-(N-octadecylcarbamoyl)-3-oxabutyryl-1,7,10,13,19-pentaoxa-4,16-diazacyclohenicosane, 165 mg NPOE and 4.8 mg K-TCPB were coated on the Ta\(_2\)O\(_5\) layer of the ISFET surfaces, respectively \([7]\)–[9]. All the ionophores and NPOE were purchased from Dojindo Laboratories. The MPC polymer was also coated on these mixture surfaces. The thicknesses of the ion sensitive membranes were 69 \(\mu\)m, 54 \(\mu\)m and 64 \(\mu\)m for the Na\(^+\), K\(^+\) and Ca\(^{++}\) cations, respectively. An Ag/AgCl electrode in agarose gel with a saturated KCl solution was used as the reference electrode.

![Fig. 2](image-url)  Fabrication process of healthcare device made of PET.

![Fig. 3](image-url)  SEM photographs of embossed microcapillary patterns on a PET plate.
Dulbecco’s phosphate buffer solution (PBS) as an electrolyte consists of 200 mg/l KCl, 200 mg/l KH$_2$PO$_4$, 8 g/l NaCl and 1150 mg/l Na$_2$HPO$_4$. The ionic strength and pH of the buffer were 160 mM and pH=7.4, respectively.

3. Results and Discussion

3.1 Issue of Concave-Shaped Defects Generation

At first, both issues of the wider pattern width and concave-shaped defects generated employing C$_3$F$_8$ alone plasma as mentioned above were considered to result from the following mechanism: The wider width etched pattern (see Fig. 4(a)) was caused by deposition of fluorocarbon polymer on the Cr mask. The defects shown in a SEM photograph inset in Fig. 5 was also presumed to be generated by the polymer deposition, that is, polymer precursors produced in the gas phase grew up during long etching time due to low quartz etch rate less than 300 nm/min. Subsequently, the particles dropped on the quartz surface, thus playing a role of masking for fluorocarbon ions bombardment. Hence, CF$_4$ as a fluorine atom source which decreased carbon/fluorine ratio in the gas phase added to C$_3$F$_8$. Figure 4 shows variation of the etched features as a function of %CF$_4$ in C$_3$F$_8$. The etched wall features were improved with increasing CF$_4$ concentration. However, since CF$_4$ alone plasma reduced etch selectivity of the Cr film to the quartz, the side wall of the masking Cr film retarded by the ion bombardment, thereby forming a tapered feature at the upper side of the trench. Eventually, a best-etched feature was obtained at 70%CF$_4$ concentration as shown in Fig. 4(c). The etch selectivity was about 20 in this condition. The number of defects decreased with increasing CF$_4$ addition as shown in Fig. 5, while considerable number of defects were still observed at the best concentration of 70%CF$_4$ in C$_3$F$_8$. We noted that the defects did not appear at a depth of a few µm, but they were observed clearly over about 10 µm depth and size of these defects was nearly same. These results suggested that a reason generating the defects was present on the original surface, because defects with different sizes should be generated if the masking was caused by the continuously deposited polymers. We tried to remove the masking materials on the quartz surface by increasing ion accelerating voltages of $V_{dc}$. The number of defects decreased dramatically with increase in $V_{dc}$, and finally the defects disappeared at $V_{dc}$=900 V, while the masking Cr films were etched considerably by the high voltage accelerated ions. Accordingly, the present issue was overcome as shown in photographs in Fig. 6(b), by the two steps process in which the quartz surface was cleaned at $V_{dc}$=820 V for 2 minutes and then etched at $V_{dc}$=500 V.

3.2 Biocompatibility of MPC Polymer

The biocompatibility of the MPC polymer was investigated by utilizing an FTIR-ATR (Fourier Transformed Infrared Attenuated Total Reflection) technique as shown in Fig. 7(a). A Si prism, both sides of which were mirror-polished at 45 degrees, was prepared for the ATR measurement. The Si surface was oxidized to real-
ize the actual capillary quartz surface. Figures 7(b) and (c) shows the time-dependent variations of the FTIR-ATR spectra for the dipped serum on the SiO$_2$ bare surface (b) and on the 0.3 wt% MPC polymer coated quartz surface (c). The sensitivities for IR absorption by adsorbed substances on the surface in the (c) case was considered to be lower than those in the (b) case because of short immerse length of the evanescent wave due to thick coating of MPC polymer. This reduction of sensitivity was already compensated in Fig. 7(c) by dividing the absorbance by the ratio of peak heights for H$_2$O, which is considered to exist at same amount per area on the surface in the both (b) and (c) cases. The (b) spectrum after dipping of the serum demonstrated adsorption due to proteins which were represented by the NH$_x$ and C=O peaks, while the proteins did not adsorb on the (c) surface. It revealed that proteins were not adsorbed on the MPC polymer coated surface. As shown in Fig. 8, adsorption of red blood corpuscles on the PET plate was also investigated for surfaces with, (a) and without the MPC polymer coating, (b), where the bare quartz surface, (c) was also checked as a reference. The present red corpuscles were obtained by centrifugation of human whole blood. A small adsorption number of 6/mm$^2$ in the case of (a) as compared with cases of (b) and (c) demonstrates that the MPC polymer coating provides a great suppression effect for adsorption of red corpuscles on the MPC polymer coating.

3.3 Measurement of Health Makers with ISFET's

Figures 9(a) and (b) show a photograph of the prototype healthcare chip made by PET plate and its schematic diagram, respectively. This chip consists of a blood inlet reservoir, a U-shaped centrifuge capillary, ISFET sensors embedded in the microcapillary chip and the electroosmosis flow (EOF) pump arranged at downstream of the sensor position. This configuration was designed to measure the health makers according to the following order; (1) PBS is filled in the whole capillary channel, (2) blood is put into the inlet, (3) it is injected into the U-shaped capillary by applying high voltage in
the electroosmosis flow pump capillary, (4) blood cells are separated by revolve the chip in the small-scaled centrifugation apparatus, (5) the obtained serum is introduced into the ISFET’s region by the electroosmosis pumping, (6) finally health makers are measured by the ISFET’s.

One of the important items for creating the healthcare chip is the measurement of health markers. In this paper, measurements of pH, Na\(^+\), K\(^+\) and Ca\(^{++}\) concentrations were tried in an actual size chip. The ion sensitive membranes coated on the ISFET sensors were relatively robust and did not peel off even after 7 days of dipping in PBS. The calibration curves of Na\(^+\), K\(^+\) and Ca\(^{++}\) cation concentrations and pH were measured in the 0.3 wt% MPC polymer-coated microcapillary. Figures 10(a)–(d) show the output voltages of each cation sensor and a pH sensor as function of concentrations obtained at 24\(^\circ\)C in the fabricated chip. Measurements were done after 4 minutes in order to wait for the output signals to be stable. It was already confirmed that the concentrations in the chips did not change by flow back within 4 minutes. Gradients of the each sensor output were \(-62\) mV/pH for pH, \(-62\) mV/pNa for the Na\(^+\) cations, \(-55\) mV/pK for the K\(^+\) cations, and \(-20\) mV/pCa for the Ca\(^{++}\) cations. These values are close to \(-59\) mV/pX (X=H, Na, K) and \(-30\) mV/pCa predicted from Nernst’s equation at 24\(^\circ\)C. The pH and concentrations of the Na\(^+\), K\(^+\), and Ca\(^{++}\) cations in the standard solution were successfully measured in such a small volume capillary.

4. Conclusion

To achieve our final goal of a creation of healthcare device, elemental technologies of the chip fabrication on polyethylene terephthalate plate (PET) have been studied. In the deep dry-etching process of quartz mold, the issues of concave-shaped defects at the bottom of grooves was overcome by the two steps process with a first step of surface cleaning at a high \(V_{dc}\) of 820 V and following step of high selective etching at low \(V_{dc}=500\) V. MPC polymer coating was studied to suppress the adsorption of bio-substance onto the inner wall and good bio-compatibility was confirmed for protein adsorption and blood cell adhesion. Micro capillaries were successfully fabricated on PET by micro molding technique. The ion concentrations of pH, Na\(^+\), K\(^+\), Ca\(^{++}\) were measured in the PET chip using embedded ISFET and crown ether ionophores.

References

Akio Oki received the B.S. degree in physics from Shinshu University in 1994 and the M. Mat. Sci. degree from Japan Adv. Inst. of Sci. and Technol. (JAIST) in 1996. He joined the Dept. of Mat. Eng., The Univ. of Tokyo, as a technical officer in 1999. He is a member of the Jpn. Soc. of Appl. Phys. and the Phys. Soc. of Jpn. His research interests are microfabrication for biochips and micro analytical system for blood analysis.

Yuzuru Takamura received his M.S. and Ph.D. degrees in Metal. and Mat. Sci. from The Univ. of Tokyo in 1992 and 1995, respectively. He joined the Institute of Space and Astronautical Science in 1996 as a research associate, and moved to The University of Tokyo in 1999. He is currently working on the development of microfluidics device for biochemical analysis. He is a member of three Japanese societies.

Takayuki Fukasawa received his M.S. degree in Chem. from The Univ. of Tokyo in 1988. He joined Tokyo Electron Ltd. (R&D center) in 1989. He moved to Tokyo Electron Yamanashi Ltd. in 1994. He received Ph.D. from The Univ. of Tokyo in July 2000. He moved to NEDO as a NEDO fellow. He has been engaged in High Density Plasma Processing of ULSI fabrication, Etching Equipment Development of SiO₂ and Si Etcher and the Healthcare Chip development. He is a member of Jpn. Soc. of Appl. Phys.

Hiroki Ogawa received M.S. and Ph.D. degrees from Musashi Institute of Technol. in 1992 and 1997, respectively. He joined Fujitsu Ltd. in 1992, and moved to a researcher of Jpn. Soc. for the Promotion of Sci. in 1997. He has been engaged in surface studies for ULSI fabrication. He is now a researcher of The Univ. of Tokyo and working on the development of the Healthcare Chips. He is a member of Jpn. Soc. of Appl. Phys. and ECS.

Yoshitaka Ito graduated from Fuku-shima National College of Technol. in 1967, and since then he has been employed by Shindengen Electric MFG. CO., LTD., working on the development of IC processes and design. Since 1977 his main fields are development of ISFET. He was awarded the First Seiyama Award of Japan Association of Chemical Sensors in 1998 for development ISFETs.

Takanori Ichiki received his M.S. and Ph.D. degrees in Metallurgy from The Univ. of Tokyo in 1992 and 1995, respectively. He joined the Dept. of Electric and Electronics Eng., Toyo Univ. in 1995, and is now an Associate Professor. He is currently working on the development of microsystems for biochemical analysis. Dr. Ichiki is a member of the AVS, and two Japanese societies.

Yasuhiro Horiike received his M.S. and Ph.D. degrees in Appl. Phys. from Waseda Univ. in 1968 and 1980, respectively. He joined Toshiba Corp. in 1968, and was appointed as Prof. at the Dept. of Electric. Eng. of Hiroshima Univ. in 1988. From 1993 until 1998, he was working at Toyo Univ., and then moved to the Dept. of Mat. Eng. of The Univ. of Tokyo in 1998. He has been engaged in LSI processes, and is currently studying on development of the Healthcare Chips. Dr. Horiike is a member of the ECS, AVS, and three Japanese societies.