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## Biochip Checking Health Condition from Analysis of Trace Blood Collected by Painless Needle

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## 1. Introduction

A healthcare chip which checks the daily condition of our health has studied by injecting trace blood into a microcapillary, measuring amount of health markers such as pH, Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>++</sup>, uric acid, lactic acid and glucose using chemical sensors. We already studied following basic technologies to create the chip; (i) fabrication of a microcapillary chip on a quartz plate [1], (ii) the inner wall coating of the bio-compatible 2-methacryloyloxyethylphosphorylcholine (MPC) polymer [2] whose surface was similar to the bio-membrane, (iii) injection of a blood serum into the capillary employing an electroosmosis (EOF) pump arranged at the downstream of the capillary and (iv) embedding ion sensitive field effect transistor (ISFET) to detect markers in the chip.

Since the blood contaminated chip should be disposal every use, however, cheap substrates are needed in place of the expensive quartz plate. Furthermore, several hundred voltages which were applied to operate the EOF pump are dangerous for the human body as well as electrostatic breakdown of the insulator used for ISFET. Therefore, in this paper, more practical healthcare chip which integrated a painless needle, ISFET, a U shape centrifugation blood separation mechanism, an EOF pump chip operated by a battery and measurement of Na<sup>+</sup> and K<sup>+</sup> ion concentrations in the blood has been studied using a cheap polyethyleneterephthalate (PET) plate.

## 2. Experimentals

The chip fabrication process was shown in Fig. 1. At first a reversal micro-channel pattern of a 30 μm x 30 μm cross section was dry-etched by the NLD (neutral loop discharge) employing a C<sub>3</sub>F<sub>8</sub>/70%CF<sub>4</sub> mixture in a quartz plate [3]. The reversal pattern was molded on a PET plate. A cover PET plate in which ISFET and the quartz made EOF pump chip were embedded was bonded on the capillary pattern molded PET. The MPC polymer was coated in inner walls of the capillary made by PET. Finally, the painless needle was connected to a blood injection inlet. The photograph of the chip and its illustration are shown in Fig. 2. The ISFET device made by the Shindengen Kogyo Corp. includes two transistors in a chip. The top gate materials were Ta<sub>2</sub>O<sub>5</sub> on Si<sub>3</sub>N<sub>4</sub>. The sensing area of each ISFET was 10 μm long x 360 μm wide. Before the embedding the ISFET to PET chip, the gates were coated with ion sensitive membrane for Na<sup>+</sup>

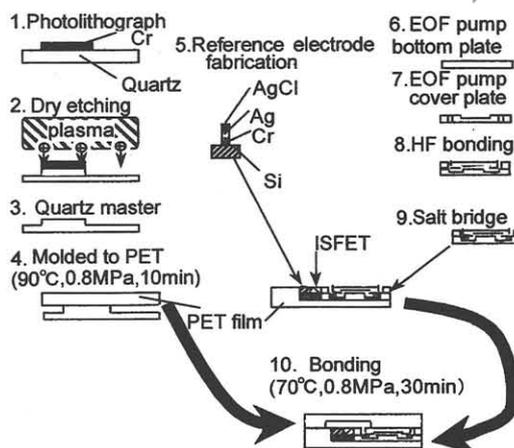


Fig. 1 Fabrication process of a plot type healthcare chip.

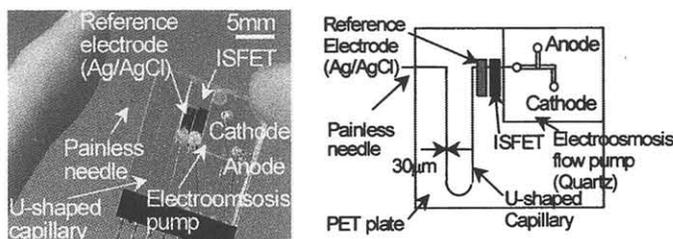


Fig.2 Photograph and illustration of a healthcare chip.

and K<sup>+</sup> sensing. Additions of bis[(12-crown-4)methyl]-2 dodecyl-2-methylmalonate and bis[(benzo-15-crown-5)-4-methyl]pimelate to acetylcellulose were used as ionophores for Na<sup>+</sup> and K<sup>+</sup> ion measurements. These ionophores were made by Dojindo laboratories. For buffer solution, Dulbecco's PBS (Dainippon Pharmaceutical Co.) was used as an electrolyte.

## 3. Results and Discussion

The needle which was necessary for collecting blood without pain was fabricated as following process; The tip of a stainless tube (SUS 304 tube, outer and inner diameters were 100 and 50 μm) was polished at an angle of 10 degree by chemical mechanical polishing and it was sharpened by electropolishing at a speed of 50 μm/sec. in a phosphoric acid by applying 7 V between the tip (+) and a Pt electrode (-). A SEM picture of the obtained needle with a sharp tip was shown in Fig.3. Indeed, all of our researchers who tried to pierce it into their skins and to extract the whole blood did not feel any pain.

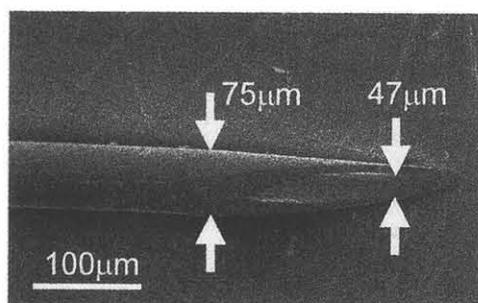


Figure 3. SEM picture of the tip of painless needle.

To transport the extracted blood in the microcapillary, a low voltage EOF pump was developed using a quartz plate. Generally, the pumping pressure of EOF is approximately inversely proportional to square of capillary diameter. Hence, decreasing capillary diameter reduces operating voltages without degrading pumping ability of pressure and velocity. The quartz plate was used simply because the surface zeta-potential, which controls the electroosmosis flow, is much higher on the quartz than that is on MPC polymer. A wide (1mm) width, short (100 $\mu$ m) length, and narrow (0.1~10 $\mu$ m) height gap channel were fabricated by dry-etching process on quartz chip as EOF pump as inset in Fig. 4. For electric contact without pressure leak, a photo-polymerizing gel was micro-fabricated as a salt bridge in the chip by photolithographic technique. As shown in Fig. 4, static pressures increased with decreasing gap size, and 125 mm

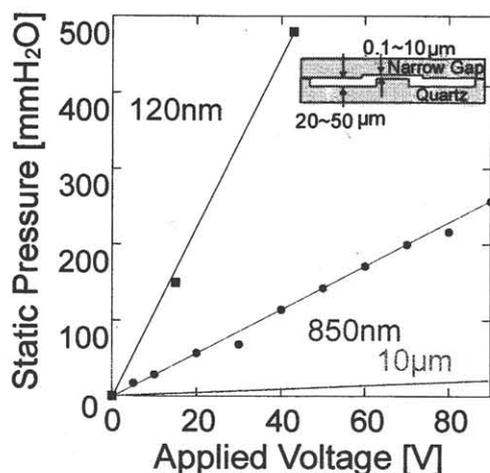


Figure 4. Static pumping pressure of quartz made narrow gap low voltage EOF pump.

H<sub>2</sub>O (~1250Pa) was obtained at 10V with 120 nm gap. In this condition, flow velocity was 100  $\mu$ m/s with a load of the 1cm capillary. This pumping ability is considered to be enough for typical microfluidics applications. The power consumption at this condition was 0.1 mW, which is 1/1000 of 10 $\mu$ m gap case for same pressure.

Finally, measurement of Na<sup>+</sup> and K<sup>+</sup> concentrations employing the chip of Fig. 2 followed the next procedure: (1) All paths in the chip were filled with 1/10 PBS. (2) Wister rat's whole blood of several ten nl was put into the

inlet reservoir. (3) The blood was introduced into the capillary by the EOF pump arranged at the downstream. (4) The serum was separated from the blood by the centrifuge separation in a U shape channel of the chip. (5) The serum was transported again by the EOF pump. As

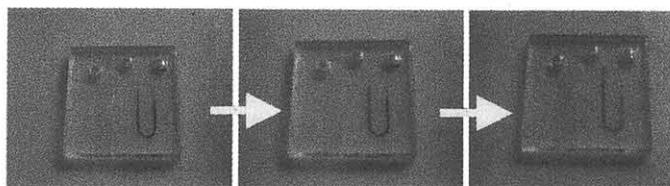


Figure 5. Transportation of serum by EOF pump.

shown in Fig. 5, one can see that the serum flows with pumping time. (6) Na<sup>+</sup> and K<sup>+</sup> concentrations in the serum were measured by each ISFET sensor as shown in Fig. 6. Here, ISFET's were operated as a constant current and voltage mode. Applied source-drain voltage (V<sub>ds</sub>) was 5V and the fixed source current (I<sub>s</sub>) was 100  $\mu$ A. The slopes

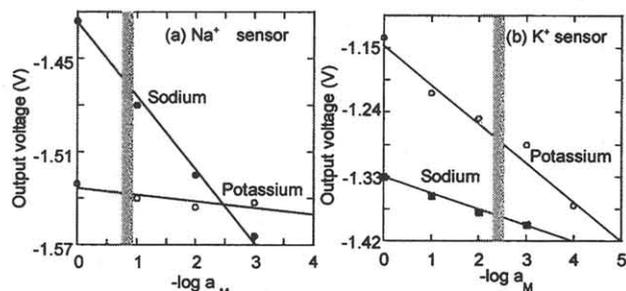


Figure 6. Calibration curve and selectivity measurements of ISFET's (a) Na<sup>+</sup> and (b) K<sup>+</sup>.

for Na<sup>+</sup>, K<sup>+</sup> are 48, 55 mV/decades, respectively. Those values are sufficiently closed to the theoretical value of 59mV/decades at 25 $^{\circ}$ C calculated from Nernst's equations. Furthermore, The tolerable selectivities of Na<sup>+</sup>/K<sup>+</sup> and K<sup>+</sup>/Na<sup>+</sup> at each sensor were obtained in a normal range of adult human.

#### 4. Conclusion

The healthcare chip has been developed by establishing basic technologies of the painless needle, the microcapillary fabrication on a cheap substrate of PET plate, the quartz made EOF pump driven by a battery, the on-chip centrifuge separation of the blood, and measurement of Na<sup>+</sup> and K<sup>+</sup> ion concentrations in the serum with ISFET. Remained issues of other marker detections, reliability, measurement system and volume fabrication technologies will be developed near future.

#### References

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