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PL-1 (Plenary)

Development of Clinical Chips for Home Medical Diagnostics

Yasuhiro Horiike[1], Akio Oki[1], Masao Nagai[2], Madoka Takai[3], Chia-Hsien Chang[1], Hideaki Hisamoto[4] and Hiroki Ogawa[2]

[1]National Institute for Materials Science, 1-1, Namiki, Tsukuba, Ibaraki, 305-0044 Japan
Phone: +81-29-860-4845 E-mail: HORIIKE.Yasuhiro@nims.go.jp
[2]Advic Inc. 1-1, Namiki, Tsukuba, Ibaraki, 305-0044 Japan
[3]Department of Materials Engineering, University of Tokyo, 113-8656, Japan
[4]Graduate School of Material Science, University of Hyogo, 3-2-1 Kouto, Kamigouri, Akou-gun, Hyogo, 678-1297 Japan

1. Introduction

The aging society proceeds rapidly in many countries, thus pressing each national total budget by a medical cost spent for persons of advanced years. Early prevention is very important for them to live a healthy life. Clinical diagnostic is one of the promising applications of μ-TAS (micro Total Analytical System) or Lab on a Chip [1], especially in a point of care setting. We are developing a healthcare chips which enable us to check our health condition by analyzing a trace amount of blood collected by a painless needle [2]. This paper reports the simple blood collection, an electrochemical measurement chip for bio-chemical items and a calorimetric measurement chip for life style-related diseases.

2. Electronic blood collection by painless needle

The needle collecting the blood should be painless. The edge of a 150μm diameter SUS tube was polished at 10 degrees for three planes. The inner wall of the tube was also polished ultra-smoothly, leading to natural collection of the blood by our blood pressure. To collect the blood by ourselves, the location of the blood vessel was visualized using a NIR (850 nm) light emitting diode array. In addition, measurement of the potential between the skin and the blood vessel allowed us to detect depth of the blood vessel. The combination led to the electronic collection. Figure 1 demonstrates actual collection using the electronic collection system, where the man does not look at his own arm, but observed a display.

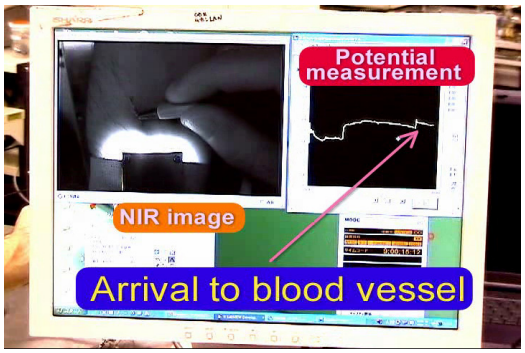

Fig. 1 Demonstration of electronic blood collection. Left; NIR image, Right; Potential variation. A person looks at the display during blood collection.

3. Electrochemistry measurement chip

We planed to measure the pH, Na^+, K^+, glucose, BUN and creatinine concentrations by an electrochemical method. The chip was fabricated by bonding two plates of a channel pattern and a screen-printed electrode patterns. Figure 2 shows this measurement chip, (a), and a magnified photograph of integrated chemical

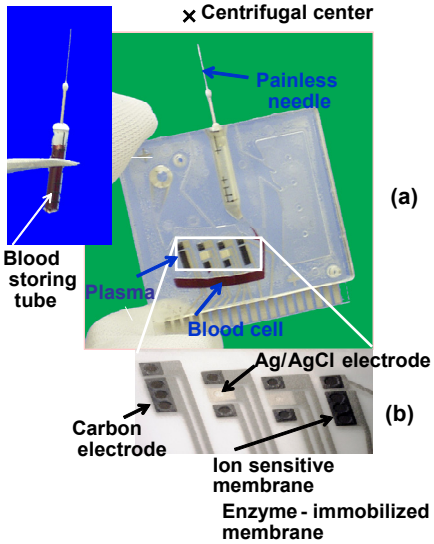

Fig. 2 Photograph of healthcare chip. A blood collected tube is inserted into the chip and centrifugall separated (a). Magnified integrated bio-censors (b)

sensors. (b). Both correction solution before the measurement and blood for the separation were conveyed by centrifugal operation, because individual blood should not be handled. The blood collection assembly was inserted into the chip after the correction and then separated to plasmas at the upper regions of the sensors and blood cells at the channel bottom.

First a non-liquid junction type KCl saturated reference electrode was developed for the electrochemical method to generate a standard potential for pontentiometric sensing. Next, Bis[(12-crown-4)methyl]-2dodecyl-2-methylmalonate and bis[(benzo -15-crown-5) -4-methyl]pimelate were used for Na^+ and K^+ ionophores. Selectivity of $Na^+/K^+=10^2$ and $K^+/Na^+=10^3$ are obtained due to the adequate anion exclusion agents. To improve the poor adhesion of glucose oxidase (GOD) at the glucose sensing, homogeneity of ferrocene was improved using VFc-co-HEMA polymeric mediator coated on a carbon electrode and chemical cross linking of glutaraldehyde on the mediater surface immobilized GOD. BUN was measured by ammonia generated from the unease reaction based on the ammonia measurement using 19-membered crown ionophore, TD19C6, PVC membranes along with anionic additives K-TCPB and TFPB, and plasticizers BBPA and TOTM. The creatinine measurement using creatine amidinohydrolase instead of unease requires more improvement at lower concentration. Now, automatic measurement of Na^+, K^+, glucose and BUN are available.

4. Calorimetric measurement chip

A hepatic function examination chip which detected γ-GTP, GOT and GPT enzymes using a calorimetric method was reported [2]. However this chip had problems such as an additional process needed for metering of plasma after the separation and high 50:1 mixing ratio of substrate buffers to plasma for GPT and GOT measurements. To solve these problems, a new calorimetric measurement chip has been developed. The chip consists of 3 layers. All process is carried out by the centrifugal force. In a 1st layer, blood separation/ plasma metering and metering of a 1st reagent are done simultaneously. Here, a long zigzag-like channel allows to separate blood cells and plasma during the transportation efficiently, thereby collecting blood cells and apportioning plasma of the top clear layer to three chambers with a definite volume of 0.4 μL. A 2nd layer conveys both plasma and 1st reagent to two reservoirs with almost same volume. A 3rd layer introduces a 2nd reagent to reservoirs, and then plasma and two kinds of reagents are injected to a measurement optical cell through a mixing channel. The mixing is performed through a long transport channel equipped with many protuberances in the inner wall which cause the chaotic advection. Figure 3 shows an experimental measurement system of the 3rd layer where a white light is incident to the optical cell. An absorbed light reflected on an Al coated cell bottom was detected by a spectrometer though a beam splitter. Not only γ-GTP, GOT and GPT, but cholesterol and neutral fat were measured successfully.

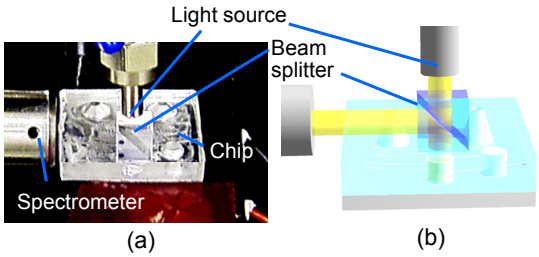

Fig. 3 Reflective optical absorption measure -ment system at the 3rd layer consisting of the mixing and the optical cell.

5. Conclusion

To establish the home medical diagnosis, a variety of clinical chips together with the electronic blood collection system have been studied. These chips will lead to preventions of life style-related diseases such as kidney trouble, diabetes and liver disease. When the home medical diagnosis system is realized, the diagnostic data communication with clinical centers through a medical network is expected to change not only medical treatment, but the society system significantly.

References

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