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System-on-fluidics immunoassay device integrating wireless radio-frequency-identification sensor chips

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A simple and sensitive point-of-care-test (POCT) device for chemiluminescence (CL) immunoassay was devised and tested. The device consists of a plastic flow-channel reactor and two wireless-communication sensor chips, namely, a photo-sensor chip and a temperature-sensor chip. In the flow-channel reactor, a target antigen is captured by an antibody immobilized on the inner wall of the flow-channel and detected with enzyme labeled antibody by using CL substrate. The CL signal corresponding to the amount of antigen is measured by a newly developed radio-frequency-identification (RFID) sensor, which enables batteryless operation and wireless data communication with an external reader. As for the POCT device, its usage environment, especially temperature, varies for each measurement. Hence, temperature compensation is a key issue in regard to eliminating dark-signal fluctuation, which is a major factor in deterioration of the precision of the POCT device. A two-stage temperature-compensation scheme was adopted. As for the first stage, the signals of two photodiodes, one with an open window and one with a sealed window, integrated on the photo-sensor chip are differentiated to delete the dark signal. As for the second stage, the differentiated signal fluctuation caused by a temperature variation is compensated by using the other sensor chip (equipped with a temperature sensor). The dark-level fluctuation caused by temperature was reduced from 0.24 to 0.02 pA/°C. The POCT device was evaluated as a CL immunoassay of thyroid-stimulating hormone (TSH). The flow rate of the CL reagent in the flow channel was optimized. As a result, the detection limit of the POCT device was 0.08 ng/ml (i.e., 0.4 μIU/ml).
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[**Key words:** Point of care testing; Immunoassay; Radio frequency identification; Flow-channel reactor; Temperature compensation]

A point-of-care testing (POCT) device is attracting growing interest in many application fields (1,2). It is intended to achieve rapid, easy-to-use, and low-cost measurements and, thereby, allow patient diagnoses in the physician's office, an ambulance, a home, or in a hospital. One of the most successful POCT applications is immunochromatography, which, for example, is widely used for diagnosing influenza and pregnancy. For the device thereof, a polymeric membrane, such as nitrocellulose, nylon or polyethersulphone, is commonly used as an immunoreaction field. A target antigen is detected by visual observation of color change induced by an immunoreaction in the membrane. The membrane-based immunoassay provides a low-cost and easy-to-use measurement instrument; however, its sensitivity and precision could not reach the level of those of a bench-top immunoassay apparatus. Owing to the large surface-area-to-volume ratio of the membrane, it is advantageous in regard to visual observation; however, it has been pointed out that its sensitivity and precision should be improved. These requirements are conflicting because certain basic restrictions are imposed on a POCT device, namely, device size, power consumption, and device cost. From the viewpoint of sensitivity, an apparatus for optical detection of color change on the membrane has been introduced. This optical reading apparatus consists of a light source (for irradiating the membrane surface) and a photosensor (for measuring reflected light). Although this configuration provides high-sensitivity measurement, it increases the cost of the measurement apparatus because it requires not only an optical sensor but also light-collection optics and a signal-processing system. To qualify as successful POCT, it is often required that sensitivity and preciseness are comparable with centralized laboratory tests and that the test device is easy-to-use and low-cost.

In this study, a novel POCT device for chemiluminescence (CL) immunoassay was developed and demonstrated. The device consists of a plastic flow-channel reactor and two wireless-communication sensor chips. For labeling specific substances, a sandwich immunoassay was adopted. In this immunoassay, primary antibodies are immobilized inside the flow-channel reactor of the device prior to target detection. A test-solution including the target antigen is then applied to an inlet of the flow-channel reactor. The antigen is captured by the primary antibody immobilized on the inner wall of the flow channel and detected with enzyme (alkaline phosphatase, ALP) labeled antibody (for CL detection). The CL is measured by a photosensor chip, which integrates photodiodes, an amplifier, an analog-to-digital converter, and a wireless

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communication circuit. Temperature of the POCT device is monitored by a temperature-sensor chip, which has the same architecture as the photosensor chip (except a temperature sensor is used instead of a photodiode). As for the wireless-communication protocol, passive communication is adopted. Data communication to an external reader is carried out and power supply is supplied by an RF field generated by the reader in a wireless manner; thus, a radio-frequency-identification (RFID) sensor chip can operate without a battery and communicate without wires. One of the main features of the developed POCT device is the RFID sensor, which is a new type of sensor combining RFID-tag technology with sensing. It detects biological targets and transmits data by RF signal. A RFID tag, as is well-known, has become very popular for merchandise control, IC smart cards issued by railway companies, and so on. Typically, commands and power to drive the RFID chip are transmitted from a reader unit, and an ID number is returned to the reader from the chip. In a similar manner, the developed RFID sensor chip returns sensed biological data to the reader. It monolithically integrates a biological sensor, an RF communication circuit, and a chip coil on a single chip. All the components necessary for the measurement and data-transmission processes (including immunoreaction, CL reaction, light-intensity measurement, temperature measurement, signal processing, and wireless-signal transfer) are merged in the POCT device, which is a result of consolidated CMOS-LSI technology. The RFID sensor chip integrating a sensor and specially designed analog/digital circuits accomplishes high sensitivity and low-production cost.

POCT devices are often used in an ever-changing environment, where temperature variation is one of the major factors in deterioration of preciseness by causing dark-signal fluctuation. Hence, temperature compensation is a key issue in regard to eliminating the dark-signal fluctuation. The temperature variation also comes from the heat due to the power consumed in the sensor chip. It brings up a temperature-induced fluctuation of the dark signal of the photodiode. In the case of laboratory-use instruments operated in a thermostatic condition, the effect of the temperature variation is negligible. However, it is common that a POCT device is subjected to variable ambient temperature. Therefore, temperature compensation is a key issue in regard to eliminating the dark-signal fluctuation.

MATERIALS AND METHODS

Sensing device A novel POCT device was specifically developed for a CL immunoassay. As for the POCT device, its usage environment, especially temperature, varies with each measurement. A two-stage temperature-compensation scheme was adopted in this study. As for the first stage, signals of two photodiodes, one with an open window and another with a sealed window, integrated on the RFID photo-sensor chip, were differentiated to delete the dark signal. As for the second stage, by using another RFID sensor chip (equipped with temperature sensor), the differentiated signal fluctuation caused by a temperature variation was compensated. The device comprises a plastic flow-channel reactor (FCR) and two RFID sensor chips, one with a photo-sensor and another with a temperature sensor. A photograph of the device is shown in Fig. 1a. A schematic cross-section perpendicular to the flow direction of the device and a block diagrams of RFID sensors are also shown in Fig. 1b and c. Fig. 2 is a magnified photograph of the RFID sensors. The FCR provides a reaction field for immune and enzyme reactions. It is made of a main substrate and an upper substrate by injection molding of cyclic olefin copolymer (COC). Sample/reagent solutions flow in the FCR by capillary force without the need for active mechanisms like micro-pumps or valves. The sensor chips and FCR are arranged for not only high optical coupling but also good thermal contact so that the temperature-sensor chip can measure the temperature of the photosensor. The RFID sensor chips integrate a signal-processing circuit, an RF wireless-communication circuit, and an antenna coil (3,4) (Fig. 2).

A two-stage temperature-compensation scheme composed of two stages (Fig. 3) was devised. As for the first stage, to delete the dark signal, signals of two photodiodes with an open window and a sealed window, integrated on the RFID photo-sensor chip, were differentiated. As for the second stage, another RFID sensor chip (equipped with a temperature sensor) was used to compensate the differentiated signal fluctuation caused by a temperature variation. As shown in Fig. 4a, the photosensor consists of two photodiodes (each with an area of 0.325 $\times$ 0.650 mm): one with an aperture for signal (PD_s) and one with metal shielding for reference (PD_r). In response to the CL irradiation, difference in cathode voltages, V_{pd1}, denoted as Eq. 1, varies, where V_{pds} and V_{pdr} are the cathode voltages of PD_s and PD_r, respectively.

$$V_{pd1} = V_{pdr} - V_{pds} \tag{1}$$

The CL captured by the photosensor induces photocurrent I_{pd1} defined by Eq. 2, where C is junction capacitance of the photosensor, and t_{ss} is signal-storage period (one second for signal measurement in this study).

$$I_{pd1} = CV_{pd1}/t_{ss} \tag{2}$$

Eq. 1 corresponds to the first-stage temperature compensation, which decreases dark current and enables long-term signal integration for weak CL intensity without saturation in amplification. However, due to the mismatch in characteristics of the PD_s and PD_r, this compensation cannot reduce I_{pd1} to zero under a dark condition. Accordingly, to compensate the residual dark current, two-stage compensation using the data from the RFID temperature-sensor chip was introduced. The analog

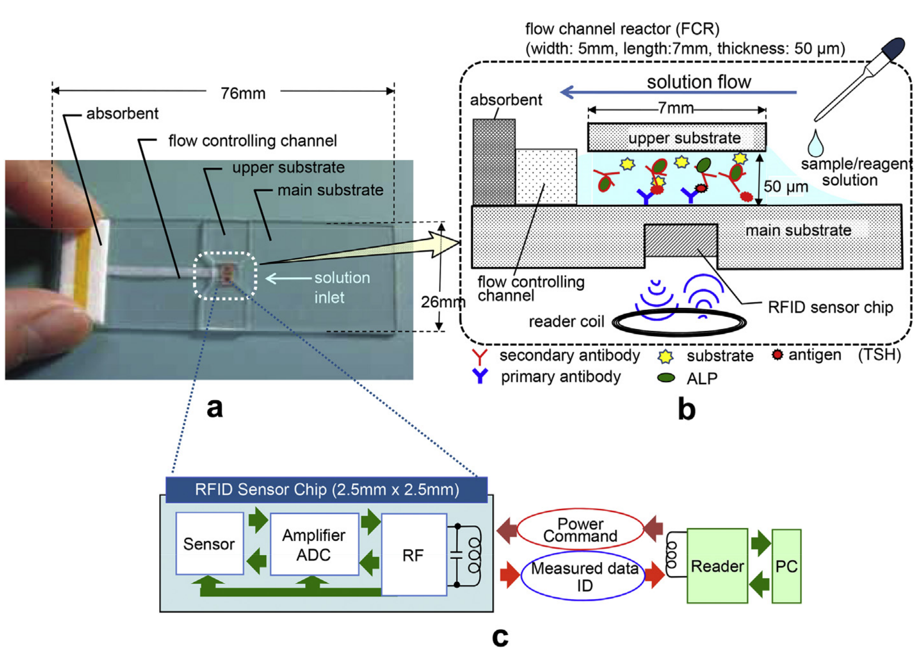

FIG. 1. Photograph of system-on-fluidics immunoassay (SOFI) device, schematic of flow-channel reactor (FCR) and block diagram of wireless RFID sensor chip.

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