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Short communication

An integrated photo-thermal sensing system for rapid and direct diagnosis of anemia

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ABSTRACT

This article presents a thermal biosensor to diagnose the anemia without chemical treatments using temperature increase of red blood cells (RBC) when hemoglobin molecules absorb specific wavelength of photons and convert them to thermal energy. For measuring temperature change of red blood cell, the micro-scaled platinum resistance temperature detector (Pt RTD) was developed. For maintenance of constant ambient temperature, we designed and fabricated a thermostat system. The thermostat system consists of a K-type thermocouple and two electric heaters that serve to increase the system temperature, which is monitored by the thermocouple. Both heaters and the thermocouple were connected to a proportional-integral-derivative (PID) controller and enabled to maintain the temperature constant ($<\pm 0.1\,^{\circ}C$). For specific heating of red blood cell, 8.0 W/cm^2 diode pumped solid state (DPSS) continuous wave (CW) laser module was used with 532 nm wavelength. Using this system, we successfully measured the temperature variations (from $66.33 \pm 2.72\,^{\circ}C$ to $74.16 \pm 2.06\,^{\circ}C$) of whole blood samples from 10 anemic patients and subsequently determined the concentration of hemoglobin (from 7.2 g/dL to 9.8 g/dL). The method proposed in this paper requires significantly less amount of whole blood sample (6 μl) compared with the conventional methods (175 μl) and allows instantaneous diagnosis (3 s) of anemia.

1. Introduction

Anemia is one of the most common blood-related diseases, globally affecting over 15% of the human population. The diagnosis of anemia is achieved by the red blood cell count, hemoglobin analysis, or mean corpuscular volume test. The state of the art is to use flow cell counting technology (Fu et al., 1999; Kim et al., 2008), colorimetric method (Kampen and Zijlstra, 1983), light-scatter measurement (Mohandas et al., 1986), etc. to measure the corresponding parameters. Among these parameters, the quantitative measurement of hemoglobin molecules can be used effectively for the diagnosis.

The existing methods for measuring the hemoglobin concentration employ hemoglobin cyanide (cyanmethemoglobin, HiCN) method (Kampen and Zijlstra, 1983), Hematocrit method, the measurement of light absorbance at the isobestic wavelength (Jeon et al., 2002), etc. Although the conventional colorimetric measurement (HiCN) is the standard method promoted by the International Committee for Standardization in Hematology (ICSH), toxic chemicals such as potassium cyanide (KCN) and dimethyllaurylamine oxide (DMLAO) must be used. On the other hand, the hematocrit method requires a large quantity of blood samples for the centrifugal separation of red blood cell and the system is difficult to miniaturize. Absorption difference at specific wavelength light method, although noninvasive, does not provide high accuracy. Therefore, in order to overcome such limitations, we now introduced the new possibility of measuring hemoglobin concentration using photo-thermal effect by laser irradiation. This employs the principle that chromophores absorb specific wavelength of photons and convert them to thermal energy (Anderson and Parrish, 1983; Almond and Patel, 1996). The pulse duration and energy are proportional to the temperature change of the target molecules (Pfefer et al., 2000; Lapotko and Ekaterina, 2005; Lapotko, 2006). Previous studies in our laboratory involved a direct measurement of hemoglobin concentrations *in vitro* using a laser irradiation system and a photo-thermal sensor (Kwak et al., 2010). In this paper, we include a newly designed thermostat system in our previous system to obtain the more precise measurement data from human samples and attempted to directly measure hemoglobin contents from 10 anemic patients without chemical solutions using photo-thermal effect of hemoglobin as shown in Fig. 1. The system featured in this paper is comprised of a micro-thermal sensor, a tailor-made thermostat, and a laser source to instantly heat up the hemoglobin

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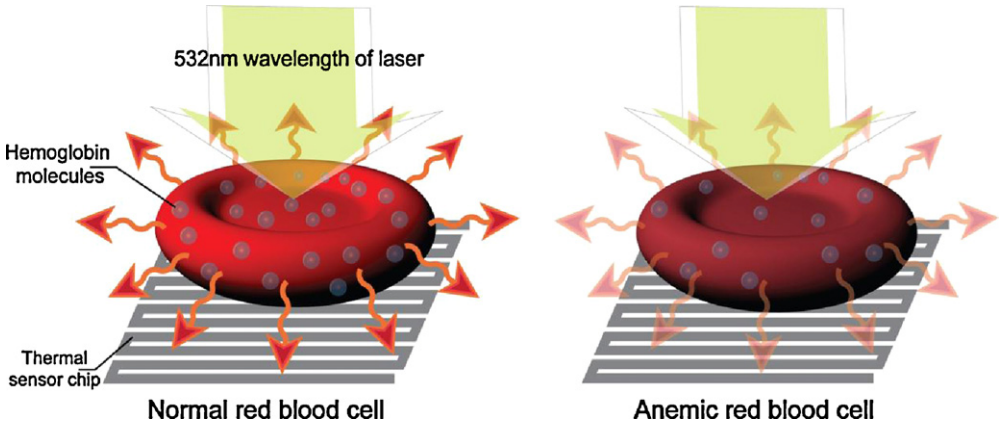


Fig. 1. Schematic diagram of photo-thermal diagnosis of anemia. The photo-thermal method uses hemoglobin concentration differences between normal and anemic red blood cell. The anemic red blood cell has low concentration of hemoglobin molecules and generates less thermal energy than normal red blood cell.

molecules, enabling an accurate and rapid diagnosis (less than 3 s) with only a small amount of sample (6 μl).

2. Materials and methods

2.1. Fabrication of micro-thermal sensor and system setup for thermal measurements

The micro-thermal sensor was fabricated using miroelectomechanical system technique (see fabrication of micro-thermal sensor in supplemental materials). By applying a more complicated system of four-wire Pt RTD configuration, a full cancellation of the resistance error due to spurious effects and lead wire resistance was provided to further increase the accuracy and reliability of the resistance being measured (Childs et al., 2000). To maintain the temperature of a reaction chamber constant is the most important factor in the measurement of the blood sample temperature variation induced by photo-thermal heating. To solve this problem, we designed and fabricated a thermostat system (see SFig. 1(c) in supplemental materials) for enable to maintain a constant temperature (<±0.1 °C). Prior to experiments, the percentage of decrease in light intensity through the 20 mm thick acryl and the 0.13–0.17 mm cover glass was measured to be 8.7% and 7.4%, respectively. Therefore, the initial light is subjected to 16.1% decrease in light intensity as it reaches the blood sample, and the light intensity was calibrated accordingly. In this experiment, the light intensity to which the blood sample was subjected was 8.0 W/cm^2.

2.2. Blood sample preparation

The blood samples were collected from a healthy male in his twenties. In order to prevent coagulation of blood samples, Liquid K3EDTA (Lavender BD Vacutainer®) was used. The erythrocytes were separated from whole blood sample using the centrifuge machine (Centrifuge MF80, Hanil Science industrial) operated at 2000 rpm for 10 min. The hemoglobin concentration of prepared blood sample was validated as 12.7 g/dL using conventional hematology system (ADVIA®2120). The hemoglobin concentration of AB plasma was validated as 0 g/dL using the same conventional hematology system. Erythrocytes were enriched by removing plasma and diluted using AB plasma as several concentrations of 0.34 g/dL, 0.67 g/dL, 1.35 g/dL, 2.7 g/dL, 5.4 g/dL, 8.1 g/dL, 10.8 g/dL, and 13.5 g/dL. With our system the temperature increase of each different concentration of the samples was measured and used for the standard curve later to determine the hemoglobin concentration of anemia patients. In total, blood samples from ten anemia patients and one healthy person were used in this experiment. Hemoglobin concentration (HGB) of the blood samples were determined using a complete blood cell count machine (ADVIA®2120) to compare with our system and summarized in Fig. 3(b).

3. Results and discussion

3.1. Characterization of micro-thermal sensor

To fabricate the micro-thermal sensor, a platinum resistive temperature detector was used in the research. Platinum is a precious metal with the most stable, linear resistance change versus temperature change, and a very good figure of merit to integrate in micro-system (Clayton, 1988; Park et al., 2003; Chung and Kim, 2008). This Pt RTD's resistance change versus temperature change can be accurately modeled by the following Callendar–Van Dusen Eq. (1) as shown below.

For the temperature range between 0 °C and 661 °C the equation is

$$R(t) = R(0)(1 + A \times t + B \times t^2) \quad (1)$$

where $R(t)$ and $R(0)$ represent resistance at t temperature and resistance at 0 °C, respectively. For platinum, A, and B are 3.893×10^{-3}, and -3.402×10^{-8}, respectively. The constants were experimentally measured. Since B is relatively small, the resistance changes are almost linear with temperature. The sensitivity is decided by the resistance at 0 °C. Also, we applied a four-wire Pt RTD configuration further to increase the accuracy and reliability of the resistance being measured. In spite of the more complicated system of four-wire configuration, it provides full cancellation of the resistance error due to spurious effects and lead wire resistance (Childs et al., 2000). The outer set of wires is used as a current path and inner set of wires is used as a voltage measurement (see SFig. 1(d) in supplemental materials).

After the fabrication of the sensor, the Callendar–Van Dusen equation was used to calculate the temperature change via the resistance change of the micro-thermal sensor. The platinum RTD surface temperature was measured using a J-type (Iron/Constantan) thermocouple (Omega Engineering, INC) bonded to the RTD surface and connected to a digital multimeter (Agilent 34970A) for data acquisition. The according temperature was 29.4 °C and the micro-thermal sensor resistance was 189.9 Ω. Using this R(29.4 °C) value, R(0 °C) was calculated to be 170.4 Ω. From this result, the aforementioned Callendar–Van Dusen equation was derived to be as the following for this experiment:

$$R(t) = 170.4(\Omega)(1 + 3.893 \times 10^{-3} \times t - 3.402 \times 10^{-8} \times t^2) \quad (2)$$

The measured micro-thermal sensor resistance (170.4 Ω) was substituted and the above equation was solved using the quadratic formula to calculate the value for temperature change at t °C.

3.2. Limit of detection volume

The deposited sample exists as a mixed phase material of plasma and red blood cells between the micro-thermal sensor and cover glass. Local heating is generated between the micro-thermal sensor and the cover glass by a laser of 2 mm diameter. The lateral conduction through the media can be neglected because the length scale to the radial direction in the media is much larger than that of the vertical direction toward the temperature sensor. In addition, the effect of natural convection in liquid media would not be significant due to the scale of liquid phase distance between red blood cells. In these conditions, as the sample volume increases, the thickness of the sample increases. The temperature increases as the sample thickness increases because there are more red blood cells which contain the Fe ions to absorb the photon energy and generate heat. However, when the thickness increases sufficiently over a certain criterion, there are sufficient number of particles between the cover glass and micro-thermal sensor. Photon energy from the 8.0 W/cm^2 laser intensity used in this experiment is transferred to thermal energy when sufficient amount of hemoglobin is present. When the amount of hemoglobin exceeds a critical amount, the temperature does not rise any further due to the shortage of photon energy. Furthermore, as the blood sample depth increases, the required volume of the blood increases, defeating the purpose of making this procedure minimally invasive. Therefore, the minimum volume of the blood sample required for the measurement has to be determined.

If the thickness of the blood sample exceeds a critical value, the photo-thermal effect only takes place on the surface. In this case, the thermal energy is transferred to the sensor by conduction, thus the actual temperature change cannot be accurately measured. Because the 532 nm wavelength laser is a visible light, it has a short penetration depth. This depth can be calculated using the following Beer–Lambert–Bouguer law:

$$T = \frac{I}{I_0} = 10^{-\alpha l} = 10^{-\varepsilon l c} \tag{3}$$

$$A = -\log_{10}\left(\frac{I}{I_0}\right) = \varepsilon L c = \alpha L \tag{4}$$

$$L = \frac{1}{\varepsilon c} = \frac{1}{\alpha} \tag{5}$$

where T represent transmissivity, I_0 and I the intensity of the incident light and the transmitted light, respectively, A the absorbance, and L the penetration depth. The incident optical intensity decays exponentially in a conducting medium. According to the above Beer–Lambert–Bouguer law, the light penetration depth is defined as the distance where the incident light field decays to $1/e \approx 0.37$ of its surface amplitude. In addition, by Eq. (5) this depth can be calculated using the inverse of absorption coefficient. Absorption coefficient of α (λ = 532 nm, C_{Hb} = 12.7 g/dL) is 62.36 cm^{-1} and the inverse value is 160.4 μm. Therefore, 532 nm wavelength laser can penetrate up to 160.4 μm of the red blood cell sample's thickness.

The photo-thermal effect according to the thickness of the blood sample solution was first investigated. Different volumes of the sample solution were placed on the surface of the micro-thermal sensor, the cover glass was subsequently placed over the sample and the laser was induced. In this experiment, we obtained a blood sample (HGB: 12.7 g/dL) from a healthy male in his twenties. Starting at 1 μl, the volume of the blood sample was increased by 1 μl up to 7 μl. All experiments were performed for 30 s: 10 for stabilizing the sample, 10 for measuring the experiment, and 10 for retention. The cover glass has 9 mm × 9 mm area and 0.13–0.17 mm thickness. The thicknesses of blood sample solution were calculated as 12.4 μm at 1 μl, 24.8 μm at 2 μl, 37.2 μm at 3 μl, 49.6 μm at 4 μl, 62.0 μm at 5 μl, 74.4 μm at 6 μl, and 86.8 μm at 7 μl sample volume.

The result of the experiment is shown in Fig. 2(a). At 74.4 μm, which is approximately half of the theoretical penetration depth of 160.4 μm, the temperature increase by photo-thermal effect reached its maximum value. When the sample volume exceeds 6 μl, no significant resistance changes of micro-thermal sensor were observed and the value saturated at 218 Ω. It is thought that as the volume of the blood sample increases, the amount of light absorbing RBC increases. This led to the increase in temperature but from 6 μl and on, it can be seen that the temperature reaches an equilibrium value (approximately at 74.1 °C). This result showed that the temperature was saturated due to the photo-thermal effect within the depth penetration limit of the 532 nm wavelength laser of 8.0 W/cm^2 intensity. This means that there was more light energy input than the amount that the light absorbing particles could absorb. Consequently, hemoglobin molecules located above the sensing area underwent the maximum absorption and the resulting temperature reached saturation value at 74.1 °C. Thus, the optimized volume of the blood sample was decided to be 6 μl. The conventional hemoglobin measurement device for anemia diagnosis requires more than 175 μl of blood sample, which is 29 times more than our method.

3.3. Determination of minimal detection time duration

After conducting experiments to find a converging plateau value of the photo-thermal effect depending on the thickness of the light absorbing sample, in which 6 μl was found to be the optimized volume of the sample, the duration of the detection time was to be optimized. The previous experiment procedure was maintained and the normal blood sample volume was changed from 1 μl to 7 μl by 1 μ at each trial. The initial thermostat temperature was set at 30 °C. At 0 s, the same 8.0 W/cm^2 intensity laser was induced on the sample. Experiments were performed for 30 s as it was done previously: 10 s for stabilizing the sample, 10 s for measuring the experiment and 10 s for retention. Each blood sample's heating is shown in Fig. 2(b), which presents the actual resistance change of micro-thermal sensor due to the photo-thermal effects, including the mean value and the standard deviation when n = 3. When 532 nm wavelength laser was induced, the sensor's resistance showed a rapid heating by which after 3 s the temperature attained a maximum value and did not show any further change. Using the 1 s time period between the 3rd and 4th second, the resistance change was converted to temperature change using the equation 2. In this setting, 1 μl sample resulted in 45.88 ± 2.51 °C, 2 μl in 59.82 ± 1.51 °C, 3 μl in 64.41 ± 1.99 °C, 4 μl in 69.98 ± 1.78 °C, 5 μl in 72.04 ± 0.88 °C, 6 μl in 74.16 ± 0.52 °C, and 7 μl in 74.18 ± 0.20 °C. This experiment shows that the time duration required for the diagnosis of anemia using a fixed amount of hemoglobin is less than 3 s, which is a significant improvement over the current state of the art. Following experiments took into consideration the laser intensity and the sample thickness uncertainties and the temperature change was measured for 2 s in between the 4th and the 6th second after the initiation of the laser. The results are represented in the graph of Fig. 2(b).

3.4. Measurement of hemoglobin contents of anemia patients' blood samples

To investigate the diagnostic capability of the system, whole blood samples from 10 anemic patients were used. The experimental conditions and set up are the same as the previous description:

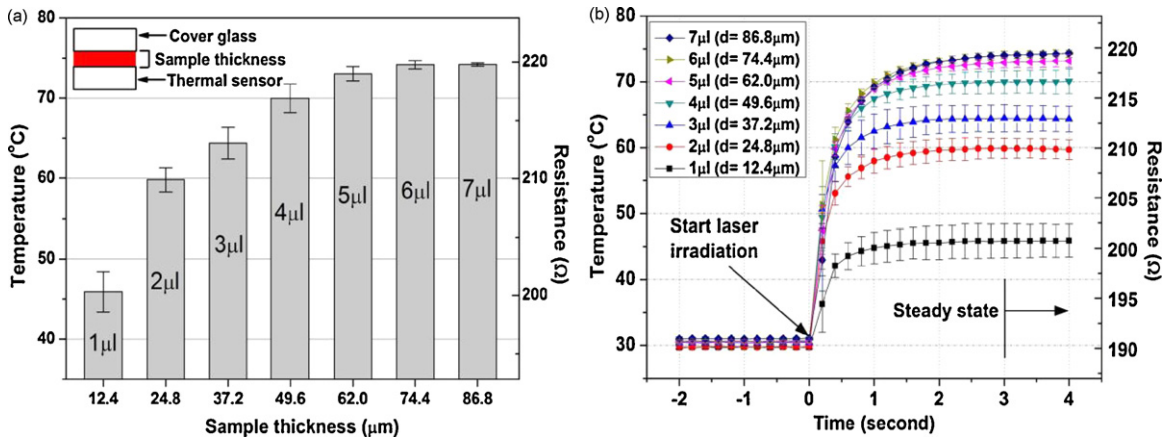
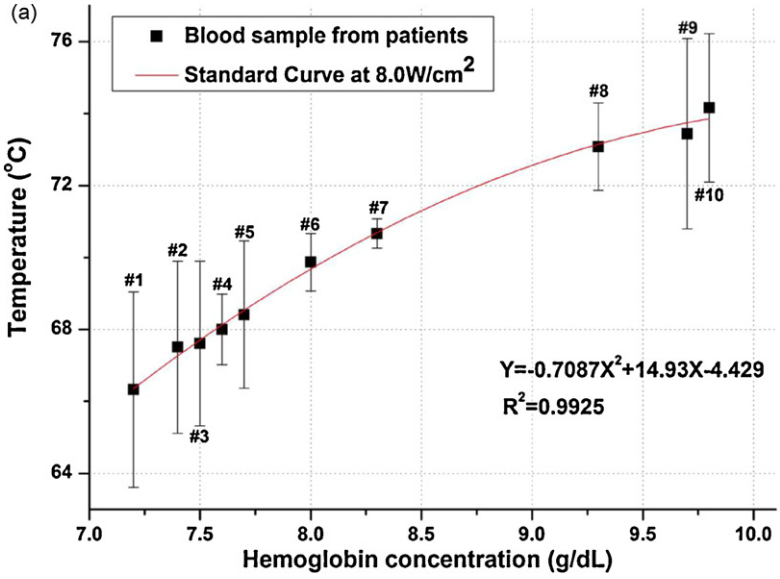


Fig. 2. (a) Maximum temperature changes of whole blood (Hb: 12.7 g/dL) by laser inducing. The sample volume represents the thickness of blood sample. Each thickness of blood sample is 12.4 μm at 1 μl, 24.8 μm at 2 μl, 37.2 μm at 3 μl, 49.6 μm at 4 μl, 62.0 μm at 5 μl, 74.4 μm at 6 μl, and 86.8 μm at 7 μl sample volume. When sample volume is over 6 μl, the maximum temperature change reaches a maximum value under the 532 nm light. The relative standard deviation (RSD) is 1 μl = 5.479%, 2 μl = 2.526%, 3 μl = 3.092%, 4 μl = 2.545%, 5 μl = 1.202%, 6 μl = 0.6967% and 7 μl = 0.2675%, 2(b) Laser induced heating behavior of whole blood (Hb: 12.7 g/dL). Within 3 s, all samples reached their steady state. The steady state point means that the temperature change ratio between the average of maximum temperature and steady state point temperature is over 99.7%.

using 6 μl whole blood samples and 30 s duration, 3 trials were run, from which the resistance value of the micro-thermal sensor was measured in between the 4th and the 6th second. The mean values along with the standard deviation are shown in the graph. Prior to the experiment, the blood samples from anemic patients were tested in the ADVIA2120® complete blood cell count machine (device currently used for diagnosis in academic labs and hospitals) for their hemoglobin concentration (HGB). The photothermal experiment results (temperature change) of the anemic blood samples are represented on Fig. 3(a). Starting from patient



(b)

	ADVIA®2120 HGB [g/dL] (A)	Photothermal Method HGB [g/dL] (B)	Difference HGB [g/dL] (|A-B|)		ADVIA®2120 HGB [g/dL] (A)	Photothermal Method HGB [g/dL] (B)	Difference HGB [g/dL] (|A-B|)
Patient #1	7.20	6.97	0.23	Patient #6	8.00	8.07	0.07
Patient #2	7.40	7.32	0.08	Patient #7	8.30	8.35	0.05
Patient #3	7.50	7.35	0.15	Patient #8	9.30	9.26	0.04
Patient #4	7.60	7.47	0.13	Patient #9	9.70	9.41	0.29
Patient #5	7.70	7.60	0.10	Patient #10	9.80	9.72	0.08

Fig. 3. (a) Experimental results of anemia samples. The temperature changes are proportional to the hemoglobin concentrations of each anemia samples. The relative standard deviation (RSD) is #1 = 4.101%, #2 = 3.540%, #3 = 3.387%, #4 = 1.441%, #5 = 2.997%, #6 = 1.145%, #7 = 0.5802%, #8 = 1.656%, #9 = 3.595%, and #10 = 2.778%, (b) Comparison of hemoglobin contents of anemic patients obtained from our photo-thermal sensing system with those from the conventional machine.

#1 up to patient #10, the temperature increases of the blood samples due to the photo-thermal effect are $66.33 \pm 2.72\,^{\circ}C$ (for HGB: 7.2 g/dL), $67.51 \pm 2.39\,^{\circ}C$ (7.4 g/dL), $67.61 \pm 2.39\,^{\circ}C$ (7.5 g/dL), $68.00 \pm 0.98\,^{\circ}C$ (7.6 g/dL), $68.41 \pm 2.05\,^{\circ}C$ (7.7 g/dL), $69.87 \pm 0.80\,^{\circ}C$ (8.0 g/dL), $70.67 \pm 0.41\,^{\circ}C$ (8.3 g/dL), $73.08 \pm 1.21\,^{\circ}C$ (9.3 g/dL), $73.44 \pm 2.64\,^{\circ}C$ (9.7 g/dL), and $74.16 \pm 2.06\,^{\circ}C$ (9.8 g/dL), respectively. As shown in Fig. 3(a) and (b), temperature changes of whole blood samples from patients are slightly larger than those obtained from the standard curve which is made from the isolated erythrocyte. This is presumably thought that hemoglobin molecules released from ruptured erythrocytes during preparation can cause the uncertain increase in temperature of the whole blood samples. Despite small discrepancy between standard curve and the experimental results the temperature change of anemia samples is proportional to the concentration of hemoglobin molecules. The relationship between the temperature change and the hemoglobin concentration is not linearly proportional, but quadratic. The reason is that the under higher concentrations, erythrocytes in the upper part of the local heating area may absorb the photon energy and generate heat while at the same time inhibiting those in the lower part. Therefore, at high enough concentrations, the temperature will reach a plateau rather than increasing without bound. Based on the data, the ΔT, which is the increase in temperature due to photo-thermal effects of hemoglobin, is calculated to be about $2.5\,^{\circ}C$ per 1 g/dL. The coefficient of correlation (R^2) between temperature and hemoglobin concentration is 0.9925. In the previous research (Kwak et al., 2010), we checked the temperature changes of various hemoglobin concentrations by inducing various intensity of 532 nm laser. Using the fitting curve formula ($0.00597X^3 - 0.37378X^2 + 7.83337X + 27.85316$, $R^2 = 0.99399$, at 8.0 W/cm^2 intensity) of previous work, we calculated the concentration of hemoglobin using the result temperature changes of this study as shown in Fig. 3(b). As shown in Fig. 3(b), the maximum difference of hemoglobin concentration between conventional machine and photo-thermal method is within 0.29 g/dL. Since the maximum allowable error of conventional machine is 0.3 g/dL, our device is sufficiently accurate to diagnosis of anemia. As a result, these results show that through quantitative analysis of light absorbing hemoglobin molecules, anemia induced by iron and hemoglobin deficiencies can be successfully diagnosed.

4. Conclusions

In this experiment, we developed a new diagnostic method for anemia, in which the oxygen transporting capability is significantly reduced due to the deficiency in hemoglobin, using the photo-thermal property of iron within the RBC, and we successfully measured the difference in the photo-thermal effect of whole blood samples with varying hemoglobin concentration from multiple anemic patients. Although, this new method has a narrow detection range (0–10.8 g/dL) compared with conventional HiCN method (0–25.6 g/dL), it is a sufficient detection range for diagnosis of anemia without chemical pretreatment process. Also, the method proposed in this paper uses significantly less amount of whole blood sample (6 μl) compared to the current technology and allows instantaneous diagnosis (3 s). Furthermore, this method enables an accurate quantitative analysis of hemoglobin regardless of the hemoglobin's location with respect to RBC, hence eliminating the need for any toxic chemical solutions used for the hemolysis of the RBC's lipid bilayer and for the conversion of hemoglobin to metheoglibin. Future applications of this technology involving photo-thermal effects of RBCs will include the measurement of deformability of single RBC due to the change in hemoglobin (Mokken et al., 1992) and the replacement of existing optical/chemical testing methods for abnormal RBCs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bios.2010.06.055.

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