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Abstract. A noninvasive glucose monitoring system based on mid-infrared, attenuated total reflection spectroscopy using a hollow optical fiber probe is developed. Owing to the flexible fiber probe, measurement of oral mucosa, where blood capillaries are near the skin surface, is possible. Blood glucose levels are measured by detecting the peak intensity of glucose absorption bands, and the experimental results showed that the reproducibility of the measurement is high enough for monitoring blood glucose. [DOI: 10.1117/1.JBO.19.5.057010]

Keywords: infrared spectroscopy; blood glucose measurement; hollow optical fibers.

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1 Introduction

Monitoring and quantification of glucose level in blood are important ongoing fields of research in clinical analysis[1] for controlling and preventing diabetes. As a substitute for conventional blood sampling by pricking a finger, a variety of optical methods based on near-infrared (NIR) spectroscopy have been proposed and developed to measure blood glucose noninvasively.[2–7] However, those systems still have accuracy and reliability problems, so they are not widely used in clinical applications. One of the reasons for these problems is that the NIR spectroscopy method analyzes detected harmonic overtones of the target molecular vibrations. In the NIR wavelength, a number of overtone peaks of other components usually overlap one another; therefore, the use of complicated multivariate statistics such as principal component analysis is necessary for quantitative analysis.

In this report, we examined a noninvasive blood glucose monitoring system based on Fourier transform infrared spectroscopy (FT-IR) in the mid-infrared (MIR) region. MIR spectroscopy detects the fundamental vibrations of molecules and this gives more distinct glucose peaks than NIR spectroscopy. To overcome the problem of limited light penetration due to large absorption coefficients, the attenuated total reflection (ATR) method is usually applied for MIR spectroscopy. In this method, a prism made of high-refractive-index materials, such as diamond and silicon, is used and the absorption of samples that are in contact with the prism surface is detected when the evanescent field produced by total reflection is absorbed. The intensities of the absorption peaks detected by the MIR-ATR method are much higher than those detected by the NIR spectroscopy, and most of the peaks are isolated. Thus, accurate and reliable measurements can be performed without complicated calculations to remove interference between the peaks. There have been many reports of applying MIR-ATR methods for blood glucose measurement including ones measuring glucose levels of whole blood,[8–10] urine,[11] and serum.[12,13] Some groups reported that they have attempted to measure blood glucose levels *in vivo* by using an ATR prism with MIR lasers[14,15] and an FT-IR spectrometer.[16] These methods mainly detect glucose in interstitial fluid that reflects the blood glucose level[17] because the penetration depth of MIR-ATR spectroscopy is limited to a few microns. Also, the area to be measured is limited to the finger tips because of the bulky measurement equipment.

To solve this problem, Uemura et al.[18] proposed using a chalcogenide glass fiber that functions as both a delivery medium for MIR light and an ATR probe and successfully measured glucose levels from the lip. However, due to the possible toxicity of chalcogenide glasses, this system is not on the market. In this article, we developed an MIR-ATR system utilizing a flexible hollow optical fiber probe. The probe was composed of an infrared hollow optical fiber with a diamond ATR prism attached to the distal end.[19] Due to the flexibility, chemical and mechanical stabilities, nontoxicity of the hollow optical fiber,[20] and the diamond prism, measurement of the glucose level in oral mucosa with high reproducibility is expected to be possible. In this work, we obtained experimental results of *in vivo* quantitative measurement of blood glucose.

2 Experiment and Results

For measuring blood glucose concentration, we used an MIR-ATR system utilizing an FT-IR spectrometer and a hollow optical fiber. As shown in the detailed setup information,[19] a hollow optical fiber based on a flexible polycarbonate tube with an inner silver reflective layer with a cyclic-olefin polymer overcoat was used for delivery of the MIR light. This type of hollow optical fiber transmits a wide range of infrared light (wavelengths of 2 to 20 μm) with low losses.[21] The inner diameter of the fiber was 2 mm, and the length was 1 m. A diamond ATR prism was attached to the output end of the fiber, the incident light was reflected twice in this prism, and then the absorption of the sample that was in contact with the prism surface was detected when the evanescent field produced by total reflection was absorbed.

Figure 1 shows the absorbance spectra of the glucose solutions in water with various glucose concentrations. For this measurement, the ATR prism was dipped in the solution, and

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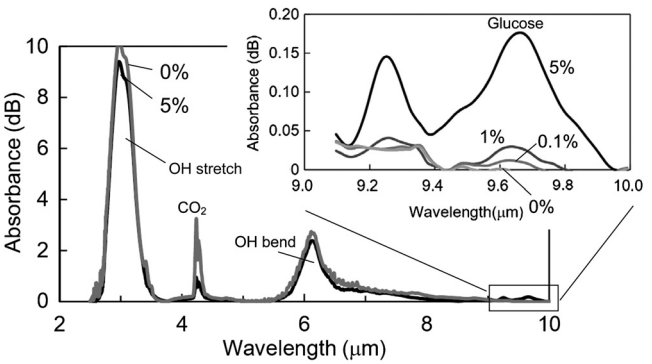

Fig. 1 Absorbance spectra of glucose solutions with various concentrations.

frequency resolutions of 4 cm^{-1} and 128 integration times were applied to obtain the spectra. Strong peaks originating from the OH stretching band and the OH bending band of water molecules appeared at about 3.0 and 6.0 μm, respectively. The infrared vibrational band assigned to glucose, which was derived from the CO stretching band, was shown at about 9.6 μm. The peak at about 4.3 μm was caused by the CO_2 gas band inside the fiber. When the glucose concentration decreased, the peak intensities of OH bands increased while the glucose peak decreased. The reason for this phenomenon is the number of water molecules on the light path increased as the number of glucose molecules decreased. Normalizing glucose peak intensity by the OH band intensities was useful when suppressing the effects of changes in the background intensity that was due to, for example, variation of the pressure on the sample surface. By taking the ratio of these peaks, only the contribution to the change in glucose level was detected. In Fig. 2, ratios of the two peaks are plotted as a function of glucose concentration. It is shown that these calculated ratios are proportional to the glucose concentration.

We also performed similar measurements with porcine whole blood, and the results are shown in Fig. 3. The hematocrit value of the sample blood was about 40%. We distinguished the glucose peak from the other blood components as shown in the figure. The peak intensity ratios of glucose to each OH band in porcine whole blood are illustrated in Fig. 4. There was a linear relationship between the peak intensity ratios and glucose concentrations, and the error was less than 5%.

Figure 5 shows the absorbance spectra of healthy oral mucosa measured *in vivo*. In this experiment, the mouth was rinsed with water to improve the adhesive properties between the oral mucosa and the prism. To clean the prism surface,

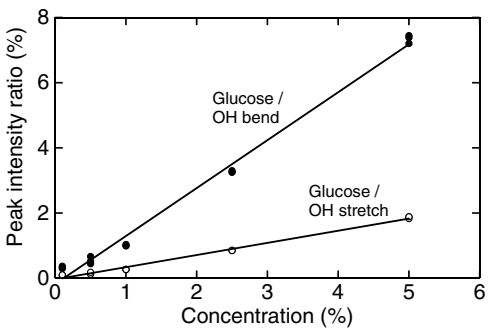

Fig. 2 Peak intensity ratios of glucose to each OH band.

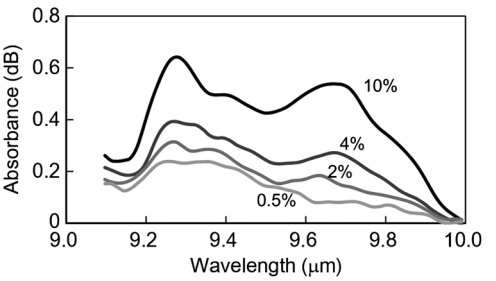

Fig. 3 Absorbance spectra of porcine whole blood with various glucose concentrations.

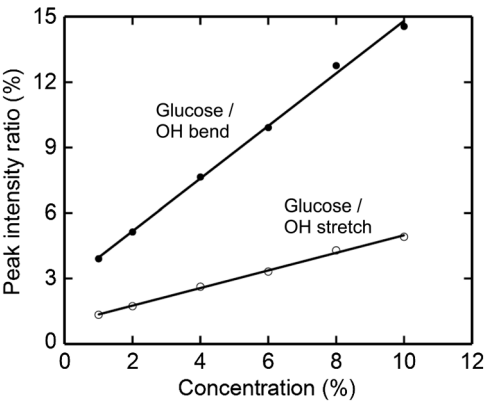

Fig. 4 Peak intensity ratios of glucose to each OH band in porcine whole blood.

the prism was washed with acetone and dried in N_2 gas for every measurement. A peak originating from glucose was confirmed at around 9.6 μm.

After a healthy volunteer perorally took 75 g of sugar, we measured the blood sugar level and infrared spectra at half-hour intervals. Reference glucose levels were measured by using a glucose sensor that was based on the puncture blood collection method. The relationship between the blood sugar levels and glucose peak intensities is indicated in Fig. 6. We found that the correlation of both values was high after repeating similar experiments.

Figure 7 shows the measured peak intensity ratios of glucose to the OH bend as a function of blood sugar level measured by the glucose sensor. The bars show the results of four

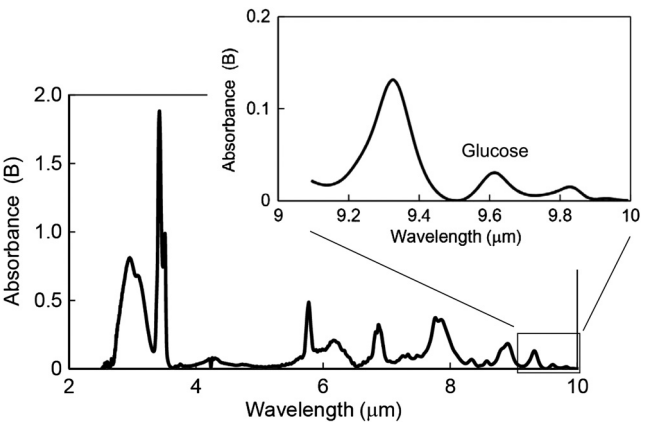

Fig. 5 Absorbance spectra of healthy oral mucosa.

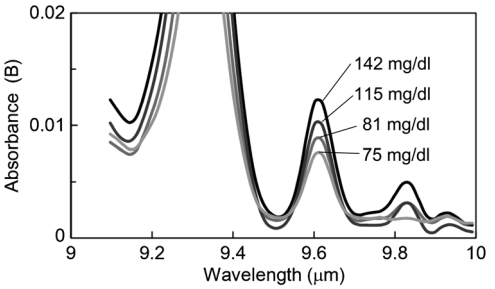

Fig. 6 Relationship between blood sugar level and peak intensities of glucose.

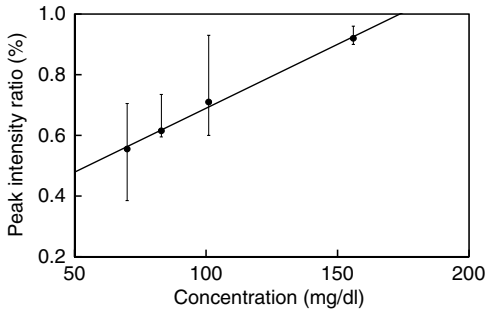

Fig. 7 Measured peak intensity ratio of glucose to OH bend peak as function of blood sugar levels.

measurements, and the dots show the averages. From these results, the measurement error was found to be around 20%.

3 Conclusion

We developed a noninvasive glucose monitoring system based on MIR-ATR spectroscopy using a hollow optical fiber probe. By measuring oral mucosa using the flexible probe, we successfully measured blood glucose levels by detecting the peak intensities of glucose absorption bands. It is known that the penetration depth of MIR-ATR spectroscopy is limited to around a few microns; thus, it is difficult to reach the blood capillary network. In our case, it is assumed that the glucose concentration measured in the interstitial fluid in the stratum strongly correlates to that of the blood. The experimental results showed that this method is useful for monitoring blood glucose, and the measurement error of *in vivo* analysis was around 20%. We suppose the main reason for this error is variation of interstitial fluid density with depth. Differences in the pressure applied to the oral mucosa caused errors that could not be suppressed by normalizing of the OH peak intensities because water is almost uniformly distributed in the depth direction. To solve this problem, we are working on developing a fiber probe with an ATR prism that has a wide detection area to obtain a uniform pressure.

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Yuji Matsuura has been a professor of the Graduate School of Biomedical Engineering, Tohoku University in Japan since 2008. His research interests include application of specialty fiber optics in medical fields, hollow waveguides for ultraviolet and infrared light, optics for soft and hard x-ray. He is a member of SPIE and the Optical Society of America.