3D printed microfluidic viscometer based on the co-flowing stream

Cite as: Biomicrofluidics 13, 014104 (2019); doi: 10.1063/1.5063425

Submitted: 27 September 2018 · Accepted: 23 December 2018 ·

Published Online: 8 January 2019

View Online

Export Citation

CrossMark

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ABSTRACT

Considering the role of viscosity in the dynamics of physical, chemical, and biological systems, accurate measurement of viscosity is essential. Although many conventional viscometers have been widely used, these conventional viscometers suffer from some drawbacks. In this study, a three-dimensional (3D) printed microfluidic viscometer was proposed based on the estimation of the pressure between two fluids to easily measure viscosity with small samples. The 3D printed microfluidic viscometer can be fabricated through amine-epoxy bonding on 3D printed blocks. By separately delivering samples and reference fluids into two inlets, an interfacial line could be induced. Based on the relation between the pressure ratio and the width of the reference flow, the viscosity (μ) of the sample can be estimated by measuring the relative width of the reference flow. The relation between the pressure and interfacial width between test samples and reference flows in the 3D printed microfluidic viscometers was analyzed by experiment and simulation to determine the effects of the mesh-like pattern of the 3D printed viscometers on the pressure estimation. To validate the proposed method, the viscosity values of glycerol mixtures measured by the 3D printed viscometer were compared with those measured by a conventional viscometer. As an application of the 3D printed viscometer, the viscosity curves for blood samples collected from diabetic and non-diabetic patients depending on their shear rates were compared. As expected, a high blood viscosity in the diabetic group was observed. Based on the experimental demonstrations, the 3D printed viscometer has strong potential to develop portable viscometers that can be translated to commercial outcomes.

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I. INTRODUCTION

Considering that viscosity is an important material property, it plays a major role in the dynamics of physical, chemical, and biological systems. Therefore, measurement of the viscosity of a material is a vital tool for analysis areas, including industrial, chemical, biological, and medical applications. For that, several conventional viscometers, including a capillary type,¹ rotating type (cone-and-plate and Coutte),^{2,3} and falling ball type,⁴ are widely used. However, these conventional viscometers suffer from some drawbacks.⁵ In the case of capillary viscometers, the flow rate and pressure in a capillary tube should be measured, and regular calibrations are necessary to verify their credibility. In addition, the conventional viscometers consume large sample quantities as a result of repetitive tests and inefficient and time-consuming procedures.⁵

In the last decade, microfluidic viscometers have emerged as alternative tools capable of addressing the abovementioned limitations of conventional viscometers.^{6–8} Nevertheless, for most microfluidic viscometers, the measured results need to be calibrated using a standard fluid as a reference. For the measurement of the viscosity of non-Newtonian fluids, additional procedures with intricate mathematical models need to be carefully performed.⁸ To address these problems, microfluidic viscometers based on the estimation of the pressure between test samples and reference fluids have been proposed.^{9–11} As representative microfluidic viscometer, micro-capillary viscometers were proposed.^{1,12,13} By measuring the interface motion, viscosity over the wide range of shear rates can be measured without the pump. However, this method has limitations including wetting defects, inability

under high shear rates, and entrance effects.⁸ A smartphone camera was used to estimate the viscosity of the sample in a glass capillary attached to the microchannel.¹⁴ By adopting multiple capillaries, parallel analysis can be possible. However, this method is not suitable for high viscosity fluids because of the small distance moved by the fluidic slug.

Considering benefits of co-flowing stream viscometers such as the simplicity of the microfluidic geometry design, sensitivity measurement, wide range of shear rates, and low sample consumption, the co-flowing stream viscometers have been extensively developed.⁸ Through the relation between the pressure and interfacial width between samples and reference flows in the co-flow stream, the viscosity variations in normal and disease models have been investigated with other biological properties.^{15–17} Recently, we proposed a hybrid method with a smartphone camera and a microfluidic viscometer to enable various applications in health-related monitoring.¹⁸ However, the microfluidic system fabricated by a combination of soft lithography and polydimethylsiloxane (PDMS) has limitations, including mechanical instability in the interconnections of PDMS and expensive infrastructure costs.¹⁹

In recent years, three-dimensional (3D) printing has gained significant interest because of the ability it gives to easily create one-off objects. Given that rapid and reproducible fabrication with 3D printing can be achieved at relatively low costs, several 3D printed microfluidic devices for fluid manipulation, separation, and point-of-care testing have been proposed.^{20,21} Commercial 3D printers can produce structures ranging from a few microns to several centimeters and print a simple microchip in 10–15 min, while more complex ones may take hours.²² The ability to rapidly realize a model is a powerful advantage of 3D printing that could be translated to commercial outcomes.²³

In this study, we proposed 3D printed microfluidic viscometers based on the pressure estimation. The relation between the pressure and interfacial width between test samples and reference flows in the 3D printed microfluidic viscometers was analyzed by experiment and simulation. To validate the proposed 3D printed viscometer, the viscosity values of glycerol mixtures measured by the 3D printed viscometer were compared with those measured by a conventional viscometer. Then, the proposed technique was applied to compare the variation in viscosities between normal and diabetic patients according to the flow rate of their blood samples.

II. MATERIALS AND METHODS

A. 3D printing

The design for the microfluidic devices was laid out in 3D using SolidWorks (Dassault Systèmes SolidWorks Corp., USA) for the preparation of geometric coordinates and converted to .stl format. Based on these coordinates, EDEN260V (Stratasys, Eden Prairie/Minneapolis, USA) head precisely printed multiple layers of the UV curable liquid polymer onto a build tray. Once the polymer spread, a UV lamp was used to solidify the liquid polymer into the hard polymer.

The T-shaped microfluidic device with a depth (H) of 100 μm consisted of a mainstream channel with a width (W) of 1500 μm and length of 14 mm and a 90° channel with a width of 500 μm and length of 7 mm. The inlet and outlet of the microfluidic device were 3D concentric structures having inner and outer diameters of 1.5 and 2 mm, respectively. To prevent a potential collapse of the main structures for mass production, the 3D printed microfluidic viscometer was divided by upper and bottom components. The 3D printed blocks were carefully cleaned with ethanol and water in a water bath sonicator.

B. Chemical gluing

After cleaning, the 3D printed blocks were bonded by chemical gluing (Fig. 1).^{24,25} The 3D printed microfluidic viscometer can be fabricated through amine-epoxy bonding on 3D printed blocks. The right side of Fig. 1(b) shows the detailed procedure of chemical gluing.²⁵ First, the surfaces of the 3D printed blocks were treated with oxygen (O_2) plasma (CUTE, Femto Science, Korea) at 40 W and a flow rate of 30 sccm (centimeters per minute at standard temperature and pressure) under a base pressure of 0.923 Torr for 90 s. After the generation of hydroxyl groups on the surfaces of two blocks, 1% (v/v) aqueous solutions of 3-Aminopropyl triethoxysilane (APTES) and 3-glycidoxypentyl trimethoxysilane (GPTMS) were poured onto the O_2 -plasma-treated blocks. After 20 min, APTES- and GPTMS-anchored blocks were washed thoroughly with distilled water and dried completely. Subsequently, the APTES- and GPTMS-anchored blocks were bonded for 1 h at 60 °C.

C. Experimental setup

The 3D printed microfluidic viscometer was mounted on an optical microscope (IX2, Olympus, Tokyo, Japan) with a 4× objective lens (NA of 0.1) and a 100 W halogen lamp as an illumination source [Fig. 2(a)]. Flows in the microfluidic device were consecutively captured by a high-speed camera (Phantom VEO710L, Vision Research Inc., Wayne, NJ, USA) at 1000 fps (frame per second). The fluid samples and reference solutions were supplied into the microfluidic device using a syringe pump (neMESYS, Centoni GmbH, Germany) with a 1 ml plastic syringe (BD; Becton Dickinson, Franklin Lakes, USA). Phosphate buffered saline (PBS) solution was used as the reference fluid to prevent bursting of the red blood cell (RBC) membranes owing to differential osmotic pressure. In this study, all experiments were conducted in an air-conditioned room in which constant temperature and humidity were remained (25 °C).

D. Numerical simulation

The numerical solutions of the fluid flow equations were obtained using CFX16.1 (ANSYS, Inc., USA). In this analysis, the flow was regarded as laminar, and a no-slip condition was applied to every wall of the microchannel. The working fluid was water at room temperature. Constant

FIG. 1 Procedure for making a 3D printed microfluidic viscometer and chemical gluing. The design for the microfluidic devices was laid out in 3D using a CAD program. To prevent a potential collapse of the main structures, the 3D microfluidic viscometer was separately printed by upper and bottom components. After that, 3D printed blocks were bonded using amine-epoxy bonding.

flow rates were applied as the inlet boundary conditions. In order to change the pressure ratio between test samples and reference flows, the flow rate at the inlet of the mainstream channel (Q_{Sample}) was varied from 0.1 to 10 ml, and the flow rate at the inlet of the 90° channel was fixed at 1 mL/h for each analysis [Fig. 3(b)]. Open conditions with a relative pressure of 0 Pa were employed at the outlet of the channel. After checking with a preliminary grid dependency test, approximately 4,500,000 nodes were used in the present study.

E. Measurement of viscosity for the glycerol mixture using a commercial viscometer

To check the measurement accuracy of the 3D printed microfluidic viscometer, glycerol mixtures with different concentrations (10%, 25%, 50%, and 70%) were prepared. The viscosities of the glycerol mixtures were measured by using a commercial viscometer (DV-II+pro, Brookfield Engineering Laboratories, MA, USA) at room temperature (25 °C); DV-II+pro measures viscous drag of a test fluid against a spindle using the deflection of a spring.

F. Blood sample preparation

Whole blood samples, drawn from patients at the Pusan National University Hospital, Busan, Korea, were collected in 4-ml BD Vacutainer® sodium heparin tubes (Becton, Dickinson and Co., Franklin Lakes, NJ) for anticoagulation. Patients were categorized in diabetic control and diabetic test groups. In each group, three patients, including two females, volunteered for the experiments. Their ages were between 20 and 60. Samples were packed in a glass capillary (75 mm long, inner diameter 1.1 mm) by a hematocrit (Ht) centrifuge (DSC-102SD, Nasco Korea) for the measurement of hematocrit. Glucose concentration in samples was measured using an Accu-Chek® sensor instrument with test strips (Roche Diagnostics, Mannheim, Germany). All experimental procedures were performed in accordance with the approved guidelines of Pusan National University's Ethics Committee.

III. 3D PRINTED MICROFLUIDIC VISCOMETER

As shown in Fig. 2(a), flow images in the 3D printed microfluidic viscometer were captured by a high-speed camera. A controllable syringe pumps precisely delivered samples and

FIG. 2 (a) Schematics of an experimental setup composed of a microscope, CMOS camera, and 3D printed microfluidic device. (b) An optical image of flows in the 3D printed channel. The T-shaped microfluidic device consists of a mainstream channel with a width (W) of $1500\ \mu\text{m}$ and a 90° channel with a width of $500\ \mu\text{m}$. The reference fluid and sample are separately injected through each inlet to induce the formation of an interfacial line between them. By averaging the optical image along the streamwise direction, a normalized intensity profile along the channel width is obtained. To accurately detect the width of the reference flow, the processed image (Processed Im) was obtained by subtracting the original flow image from the background image (BG Im). Two optical images around the confluence region were inserted in the figure. (c) Variation in the pressure ratio between the sample (PBS) and reference (labelled PBS) according to the relative width of the reference flows ($W_{\text{Reference}}/W$). A fitting curve equation [Eq. (3)] was determined by conducting a regression analysis.

reference fluids through each inlet of the 3D printed device. In the post-confluence channel, an interfacial line between samples and reference fluids was produced. Since the viscosity of the sample can be estimated based on the pressure estimation in the post-confluence channel of the T-shaped channel relation, the relation between the interfacial width and the pressure ratio between samples and reference flows

should be determined. When it was assumed that the flow is the simple Poiseuille flow in the rectangular microchannel with infinite aspect ratio, the pressure (P) can be expressed by the following equation:²⁶

$$P = \frac{12\mu QAL}{H^3W}, \quad (1)$$

FIG. 3 (a) A simulation result depicting the contour map of the velocity magnitude in the T-shaped microfluidic device under the same flow rates of a sample and reference ($Q_{\text{Sample}} = Q_{\text{Reference}} = 1\ \text{mL/h}$). Stream lines for the sample and reference flows are labeled by different colors. (b) Variations in the interfacial line between the sample and reference flows according to the flow rate of the sample (Q_{Sample}). (c) The pressure ratio of both flows ($P_{\text{Sample}}/P_{\text{Reference}}$) according to the relative width of the reference flow ($W_{\text{Reference}}/W$). (d) The relative width of the reference flow obtained from the simulation was depicted with that obtained from the experiment.

where μ and Q indicate the viscosity and flow rate of a specific fluid, respectively. ΔL , H , and W are the characteristic length, depth, and width of the rectangular channel, respectively. Considering that the sample and reference solution flow in the same channel, the pressure ratio ($P_{\text{Sample}}/P_{\text{Reference}}$) between them can be expressed as follows:²⁷

$$\frac{P_{\text{Sample}}}{P_{\text{Reference}}} = \frac{\mu_{\text{Sample}}}{\mu_{\text{Reference}}} \frac{Q_{\text{Sample}}}{Q_{\text{Reference}}} = f\left(\frac{W_{\text{Reference}}}{W}, \frac{H}{W}\right), \quad (2)$$

where the subscripts Sample and Reference indicate the properties for the samples and reference fluids, respectively. The pressure ratio is a function of the relative width of the reference flows and aspect ratio: $f(W_{\text{Reference}}/W, H/W)$. Although f is a complex function, f is simply dependent on the width ratio when microchannel is a thin slit or flow is one dimensional.²⁷

To estimate the pressure of the sample flow from the width ratio, it is necessary to accurately measure the width of the reference flow in the post-confluence channel. As shown in Fig. 2(b), the optical image of the interfacial lines between the sample (PBS) and reference (PBS labeled with rhodamine B dye) had a mesh-like pattern. This pattern is mainly caused by the fact that our 3D printer jets layers of liquid photopolymer onto a build tray using UV. The right side of Fig. 2(b) shows a normalized intensity profile along the channel width that can be obtained by averaging the flow images along the streamwise direction. Owing to the mesh-like pattern, it is difficult to directly distinguish the reference flow from the whole channel. For accurate detection of the width for the reference flow, a processed image (Processed Im) was obtained by subtracting the original flow image from the background image (BG Im). As the image intensity for the labeled PBS had a significantly lower value compared with that for the background image, the width ($W_{\text{Reference}}$) of the reference flow could be easily determined using the processed image.

To define the relation between the pressure ratio and the width ratio for the reference flow, the flow rate of the sample (Q_{Sample}) is controlled from 0.1 to 10 mL/h when the flow rate of the reference flow ($Q_{\text{Reference}}$) was fixed at 1 mL/h [Fig. 2(c)]. The flow rate of the reference flow (1 mL/h) was selected based on the flow stability and the injecting time of the syringe pump with a 1 ml plastic syringe through preliminary experiments. The range of flow rate for the sample flow is determined to avoid diffusion-induced blurring at very low shear rates and hydrodynamic instabilities at very high shear rates.²⁷ Given that the viscosities of labeled PBS and PBS solutions are the same, the ratio of the flow rates was equal to the pressure ratio based on Eq. (2). As shown in Fig. 2(c), the pressure ratio for the sample ($P_{\text{Sample}}/P_{\text{Reference}}$) exponentially decreased with the relative width of the reference flows ($W_{\text{Reference}}/W$). To determine the relation between the pressure ratio and the width ratio, the following fitting equation

was applied to the experimental results:

$$f\left(\frac{W_{\text{Reference}}}{W}\right) = a \times e^{b \times \left(\frac{W_{\text{Reference}}}{W}\right)} + c \times e^{d \times \left(\frac{W_{\text{Reference}}}{W}\right)}. \quad (3)$$

These four fitting parameters could be determined through a regression analysis ($a = 25.63 \pm 2.01$, $b = -15.58 \pm 2.12$, $c = 7.90 \pm 1.67$, $d = -4.44 \pm 0.44$). By inserting Eq. (3) into Eq. (2), the unknown viscosity of the sample can be evaluated using the following expression:

$$\mu_{\text{Sample}} = \mu_{\text{Reference}} \times f\left(\frac{W_{\text{Reference}}}{W}\right) \times \frac{Q_{\text{Reference}}}{Q_{\text{Sample}}}. \quad (4)$$

IV. RESULTS AND DISCUSSION

A. Comparison of pressure estimation between experiment and simulation

Figure 3(a) shows the flow distribution in the T-shaped microfluidic device simulated using commercial software with the same flow rates for the sample and reference ($Q_{\text{Sample}} = Q_{\text{Reference}} = 1$ mL/h). Around the confluence region, flow disturbance and acceleration are observed. In order to check the relation between the width of the reference flow and the pressure ratio of both flows obtained through the experiment, an interfacial line between the sample and reference flows was visualized by simulation [Fig. 3(b)]. As the flow rate of the sample flow increases when the flow rate of the reference flow is fixed at 1 mL/h, the width of the reference flow is significantly reduced. Figure 3(c) shows the pressure ratio of both flows ($P_{\text{Sample}}/P_{\text{Reference}}$) according to the relative width of the reference flow ($W_{\text{Reference}}/W$). As expected, the pressure ratio rapidly increases when the relative width of the reference flows decreases from 0.3. For each pressure ratio of both flows, the relative width of the reference flow obtained from the simulation was depicted with that obtained from the experiment [Fig. 3(d)]. The simulation results are in accordance with the experimental results. Based on these results, we concluded that the width of the reference flow can be accurately detected from the experimental images processed by subtracting the original flow images from the background image.

B. Validation of the 3D printed microfluidic viscometer using a glycerol mixture

For the experimental studies on fluid viscosity, aqueous glycerol solutions are commonly used.²⁸ Figure 4(a) shows a schematic diagram representing the validation test of the 3D printed microfluidic viscometer using a glycerol mixture. The glycerol mixture and reference (labeled PBS solution) are delivered in the microfluidic channel through each inlet. Flow rates of both solutions were fixed at 1 mL/h. The bottom of Fig. 4(a) shows optical images in the region of interest (ROI) of the post-confluence channel depending on the glycerol concentration. Although the flow rates are fixed, the noticeably high viscosity of the glycerol reduces the width of the reference flows as the glycerol concentration

FIG. 4 (a) Schematic of the measurement of a glycerol mixture with various concentrations. An interfacial line formed between the glycerol mixture and reference (labeled PBS solution) by separately delivering through the two inlets of the microfluidic device. Optical flow images of the glycerol mixture and reference solution in the region of interest (ROI), according to the glycerol concentration (10%, 25%, 50%, and 70%). (b) Comparison of the viscosity values for the glycerol mixture measured by the 3D printed viscometer ($Viscosity_{Chip}$) and commercial Brookfield viscometer ($Viscosity_{DVII+pro}$). (c) Bland–Altman plot between them. The horizontal axis represents the mean viscosity values measured by the two techniques, and the vertical axis shows the difference between the viscosity values measured by the two techniques. The bold and dashed lines denote the mean value and 95% limits of agreement, respectively. (d) The uncertainty variance ($[Viscosity - Viscosity_{exact}] / Viscosity_{exact}$) depending on the glycerol concentration. It is assumed that the viscosity measured by the Brookfield viscometer can be considered an exact viscosity for the glycerol mixture. The variance is determined by changing threshold value in the determination of the reference width.

increases. To validate the measurement accuracy of 3D printed viscometers, the viscosities of the glycerol mixtures measured using the proposed method ($Viscosity_{Chip}$) were compared with those measured by the Brookfield viscometer ($Viscosity_{DVII+pro}$). For each glycerol concentration, the viscosity values measured by the proposed method coincided with those measured by the Brookfield viscometer, with a high value of $R^2 = 0.999$ [Fig. 4(b)]. For a more detailed comparison, a Bland–Altman analysis, used to determine the similarity between two different data sets, was applied [Fig. 4(c)].²⁹ This analysis shows the difference between the viscosity values measured by the two methods according to their mean values that calculates the means difference between two measurement methods ($Viscosity_{Chip} - Viscosity_{DVII+pro}$) and $\pm 95\%$ limits of agreement.³⁰ As the presentation of data in the 95% limits indicates that the two methods are well matched, the viscosity values measured by the 3D printed viscometer are in a good agreement with the viscosity measured by the Brookfield viscometer.

As the viscosity is estimated based on the interfacial width ratio of the reference flow, the viscosity measured by the proposed method is significantly affected by the measurement of the interfacial width. Although the additional image processes were applied to the original images to improve the detection accuracy of the width of the reference flow, some pixels can be overestimated or underestimated near the interface. In order to check the measurement uncertainty caused by misreading the interfacial width, the uncertainty variance ($[Viscosity - Viscosity_{exact}] / Viscosity_{exact}$) was analyzed by calculating the viscosity based on the width of the reference flow obtained by different image processes [Fig. 4(d)]. For this calculation, we assumed that the viscosity measured by the Brookfield viscometer could be considered to be an exact value for a glycerol mixture. As the concentration of glycerol increased, the uncertainty variance increased. However, all of the percentage errors were in the range of $\pm 5\%$. These validation results demonstrated that the 3D printed viscometer could reasonably be used to measure the viscosity of test samples.

FIG. 5 (a) Comparison of the hematocrit between control and diabetic patients. (b) Variation in viscosities of blood samples for control and diabetic patients according to the flow rate. Measurements were completed within 12 h after blood collection.

C. Variation in blood viscosity for control and diabetic patients

Among blood components, including RBCs, leukocytes, platelets, and protein macromolecules, RBCs mainly dictate the hemorheological properties of blood because of their large proportion in the blood. They tend to form rouleaux and 3D networks by aggregating under low shear rate conditions. In contrast, a high shear force induces the dispersion of rouleaux and the deformation and rotation of RBCs.³¹ These behaviors mainly contribute to a shear thinning effect of the blood viscosity, which varies depending on the shear rate. An increase in blood viscosity augments the flow resistance and wall shear stress, which mechanically stimulates the endothelial cells of blood vessels. In many previous studies, hemorheological changes and abnormal endothelial functions lead to the development of microvascular complications.^{32–34} For these reasons, an easy and accurate measurement for blood viscosity is important for the detection of cardiovascular diseases (CVDs).³⁵

As an application of the 3D printed microfluidic viscometer, the variation in blood viscosities between control and diabetic patients was monitored. As hematocrit (Ht), the volume percentage of RBCs in blood, significantly changes blood viscosity, its levels in blood samples for normal and diabetic patients were measured by packing the blood samples using a hematocrit centrifuge [Fig. 5(a)]. Although the mean value of the hematocrit for control (0.47) was slightly higher than that for the diabetic patients (0.40), statistically a significant difference between the two groups was not observed. Blood glucose for the normal group (108.9 ± 6.4 mg/dl) is significantly lower than that for diabetic patients (210.1 ± 15.3 mg/dl).

To measure the blood viscosity depending on the shear rate, the flow rate of each blood sample and a PBS solution in a microfluidic channel varied from 0.1 mL/h to 10 mL/h. Because of the shear thinning effect of blood, the width of blood in the channel was reduced as the shear rate increased. As expected, the viscosity of blood for the control patients

increased with a decrease in the flow rate [Fig. 5(b)]. Compared to the control patients, the diabetic patients exhibited a noticeable increase in blood viscosity under a low flow rate condition. The elevated blood viscosity of the diabetic patients may be attributed to an increase in soluble thrombomodulin, von Willebrand factor, and fibrinogen owing to abnormal glucose concentrations.^{17,36} These results are in accordance with previous studies.^{37,38}

The 3D printed microfluidic viscometer has several extraordinary advantages. First, it is easy to modify the design of the viscometer because of low infrastructure costs and ease of manufacture. Second, the viscometer can reasonably estimate the variation in the viscosity of a non-Newtonian fluid depending on the fluid's shear rate. This concept suggests the high potential of 3D printing for the development of portable viscometers. In addition, the low production costs of plastic materials and easy fabrication processes are powerful for translation of this process to commercial outcomes. For this reason, making the 3D printed microfluidic viscometer could enable greater access to a high-quality viscosity measurement method that could be used anywhere.

V. CONCLUSION

We proposed a 3D printed microfluidic viscometer for the measurement of viscosities of test samples depending on their shear rates. In order to check the performance of the 3D printed viscometer, the interfacial width of the reference flow visualized by simulation was compared with that from the experimental images, and the viscosities of aqueous glycerol mixtures measured by the proposed method were compared with those measured by a Brookfield viscometer. The results indicated that the 3D printed viscometer can reasonably measure the viscosity of test samples. Then, the proposed method was applied to monitor the variation in viscosities of blood samples from diabetic and non-diabetic patients. The results proved that the viscosity variation in a blood sample can be distinctly distinguished using the 3D printed viscometer with a small sample volume. Based on the

experimental demonstrations, the 3D printer has a strong potential for use in the fabrication of portable viscometers that can be translated to commercial outcomes.

ACKNOWLEDGMENTS

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea Government (MSIP) (Nos. NRF-2016R1C1B2014255 and 2017R1C1B5018423).

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