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Generation of digitized microfluidic filling flow by vent control

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ABSTRACT

Quantitative microfluidic point-of-care testing has been translated into clinical applications to support a prompt decision on patient treatment. A nanointerstice-driven filling technique has been developed to realize the fast and robust filling of microfluidic channels with liquid samples, but it has failed to provide a consistent filling time owing to the wide variation in liquid viscosity, resulting in an increase in quantification errors. There is a strong demand for simple and quick flow control to ensure accurate quantification, without a serious increase in system complexity. A new control mechanism employing two-beam refraction and one solenoid valve was developed and found to successfully generate digitized filling flow, completely free from errors due to changes in viscosity. The validity of digitized filling flow was evaluated by the immunoassay, using liquids with a wide range of viscosity. This digitized microfluidic filling flow is a novel approach that could be applied in conventional microfluidic point-of-care testing.

1. Introduction

As quality of life improves with the growth of the population and the aging of society, there are increasing demands for health care (Peeling and Mabey, 2010). Society favors high-quality personal health care, especially fast but accurate diagnostic tests. Point-of-care (POC) testing, performed in the clinic to facilitate a prompt clinical decision regarding patient management, has been raised as a solution (Luppa et al., 2011). In the past, POC tests were performed in the physician's office equipped with bulk equipment and conducted by trained professionals (Haeberle and Zengerle, 2007; Martinez et al., 2010). Recently advanced POC tests can provide quick results to patients even without the involvement of trained professionals (Choi et al., 2004; Kulinsky et al., 2012; Price et al., 2004; Wang, 2006). These tests have received attention for their advantages of low cost, low consumption of reagents and samples, portability, and rapid turnaround (Cho and Paek, 2001; Fernández-Sánchez et al., 2005; Leung et al., 2005; Lou et al., 1993). Microfluidic technology has been integrated with POC testers, to provide a quantitative readout and to allow the handling of various samples including blood plasma, urine and saliva.

Blood plasma is an easily obtainable clinical sample containing biomarkers (Nedelkov et al., 2005). It has been widely used as a sample for quick, easy and quantitative microfluidic POC immunoassays (Dittrich and Manz, 2006; Song et al., 2003; Verpoorte, 2002). Biosite Triage® Cardiac Panel is a prominent commercial platform adopted in the clinic, and allows the quantified measurement of troponin I, myoglobin and cardiac markers in blood plasma (Linder, 2007). Blood plasma enters a microfluidic POC device under the effect of a capillary force, and is then stopped for a period by a time gate to ensure a sufficient time of reaction between the antibody on the device and the antigen in the plasma (Fischer et al., 2001). The reaction has linear correlation with time, (Lövgren et al., 1991; Reverberi and Reverberi, 2007; Vashist et al., 2015) and a wide range of blood plasma viscosity (1.10–2.09 cP at 37 °C, varying according to physical conditions, age and sex [Table S1]) affects the plasma filling and the reaction time, resulting in quantification errors. The capillary filling is passive, which can minimize the complexity of external packaging and the dead volume of the liquid sample (Zimmermann et al., 2007); in this way, capillary filling is similar to other passive methods of surface tension (Berthier and Beebe, 2007) and vacuum suction (Hosokawa et al., 2006). However, the passive controls cannot regulate flow filling sequences. The flow is not adaptable to a variation in the liquid viscosity. The sample volume, filling time and filling velocity are not adjustable but are instead completely fixed by the initial channel structure. Active flow control methods were expected to minimize the errors (Gervais et al., 2011; Pennathur, 2008). However, they require complicated and sometimes expensive external supplements (Gervais et al., 2011) to control a syringe pump, electroosmotic flow (Ramsey and Ramsey, 1997), centrifugation (Duffy et al., 1999) or electrowetting (Sista et al., 2008).

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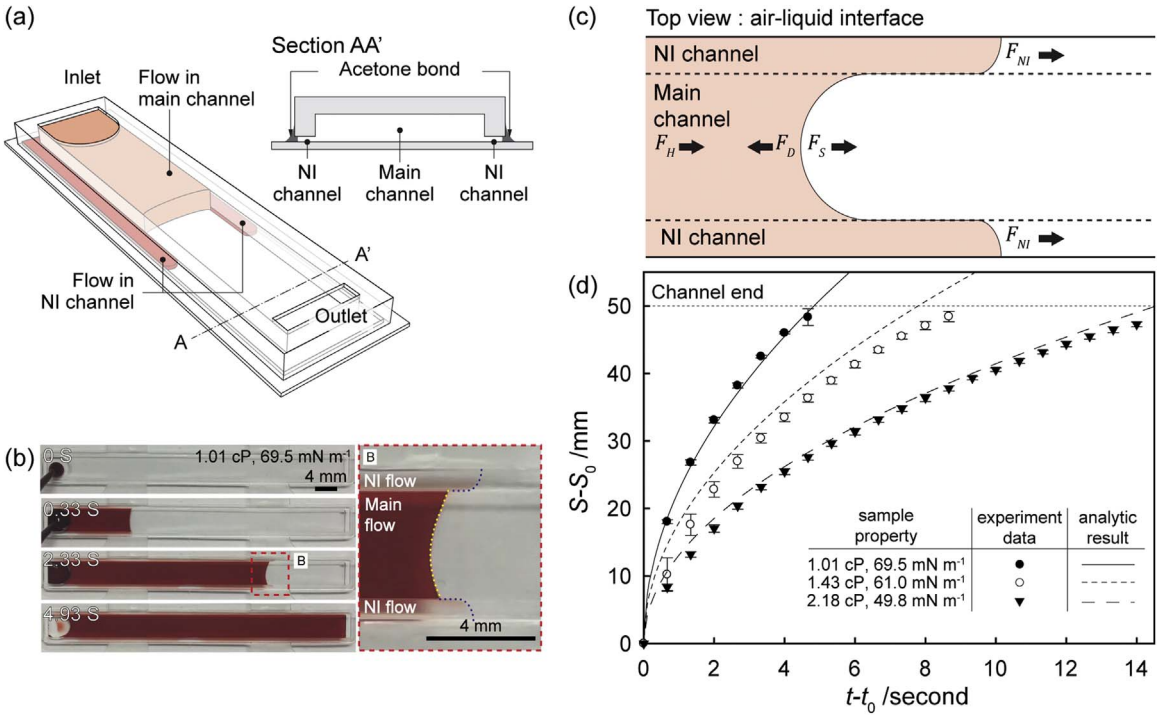

Fig. 1. NI-driven filling of a microfluidic channel. (a) Schematic illustration of the NI-driven filling. (b) Air–liquid interface in the NI-driven filling (1.01 cP, 69.5 mN m^{-1}). The yellow and blue dotted lines indicate the air–liquid interface in the main and NI channels. (c) Force balance at the air–liquid interface. (d) Graph showing the NI-driven filling displacement for liquids of varying viscosity (n=3, error bars indicate standard deviations). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The syringe pump does not require feedback control but suffers from a large dead volume and flow hysteresis. The flow rate range is limited by the syringe volume and diameter, and is not flexible or easily adjustable. Bubbles easily form when the sample amount is too small. Other methods of electroosmotic and centrifugation require complicated imaging and feedback controllers. The active methods are difficult to minimize. The present study suggests a new flow velocity control method of realizing identical and digitized capillary filling for liquids of varying viscosity, using a simple and cheap vent control. Nanointerstice (NI)-driven filling (Chung et al., 2009; Kim et al., 2014) is first applied to ensure fast and robust liquid filling. The initial filling velocity was measured employing a two-beam refraction method, and the flow filling was then digitized by the vent control. The digitized flow is independent of viscosity and easily adjustable using the signal frequency and period.

2. Material and methods

2.1. Fabrication of an NI integrated microfluidic channel

Top and bottom plates of simple microfluidic channels were prepared by the injection molding of polymethyl methacrylate. The top plate had a main channel with a width of 4 mm, height of 0.1 mm and length of 50 mm, surrounded by a wall 0.75 mm wide. Both plates were fabricated and supplied by a local company (NanoEnTek, Seoul, Korea) and bonded employing an in-house acetone injection bonding method (Fig. S1). The top and bottom plates were pressed using a customized press at 0.5 MPa, and 1.5 μl of acetone was injected at six points around the channel wall. The injected acetone covered and dissolved only the outside of the side wall. After 35 s, the applied pressure was removed and the unbounded interface of the side wall formed NIs. The final heights of the main channel and NIs, measured by a three-dimensional optical profiler (SENSOFAR Plu S neox, Kimsoptec, Seongnam, Korea), averaged 103.2 and 6.5 μm, respectively.

2.2. Preparation of liquid samples with varying viscosity

Polyethylene glycol (PEG; 25322-68-3, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in 1X phosphate buffered saline solution (1XPBS, 17-516 F, Lonza, Walkersville, MO, USA) at concentrations of 0, 25, 50, 75 and 100 mg ml^{-1}. The viscosities of the prepared PEG solutions were 1.01, 1.15, 1.43, 1.83 and 2.18 cP (centipoise), as measured by a viscosity meter (MCR-301, Anton Paar, Austria). The surface tension of PEG solutions at 0, 50 and 100 mg ml^{-1} was 69.5, 61.0 and 49.8 mN m^{-1}, respectively, as measured by a tensiometer (DCAT11, Dataphysics, Germany).

2.3. Controller for digitizing the microfluidic NI-driven filling flow

To measure the NI-driven filling velocity, two infrared lasers (CPS198, Thorlabs, Newton, NJ, USA) were installed above the NI-integrated microfluidic channel at a tilted angle (Fig. S2). One photodiode (FDS100, THORLABS) was installed beneath the channel. Velocity of the NI-driven filling was measured when air-liquid interface passes through the two infrared lasers. A solenoid valve (225T021, Neptune Research, NJ, USA) was connected to the outlet of the channel. The valve was left open until the velocity of the filling flow was measured. The valve was then closed at an application of 12 voltages, and the open/close cycle was repeated with time 5–30 and 5–20 ms respectively.

2.4. Dopamine dotting in the NI-integrated microfluidic channel

Dopamine hydrochloride powder (62-31-7, Sigma-Aldrich) was dissolved in 10 mM of Tris-HCL buffer at pH 8.5 (T2093, Biosesang, Seongnam, Korea) and a concentration of 2 mg ml^{-1}. A 5 μl volume of dopamine solution was dotted on the top plate of the channel 10 mm from the inlet, and was incubated in a humid chamber at room temperature for 4 h. After washing five times with deionized water, the channel was dried overnight at room temperature.