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Self-Powered One-Touch Blood Extraction System: Novel Polymer-Capped Hollow Microneedle Integrated with Pre-Vacuum Actuator

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Complete List of Authors:	Li, Cheng Guo; Yonsei University, Department of Biotechnology Dangol, Manita; Yonsei University, Department of Biotechnology Lee, Chang Yeol; Yonsei University, Department of Biotechnology Jang, Mingyu; Yonsei University, Department of Biotechnology Jung, Hyungil; Yonsei University, Department of Biotechnology

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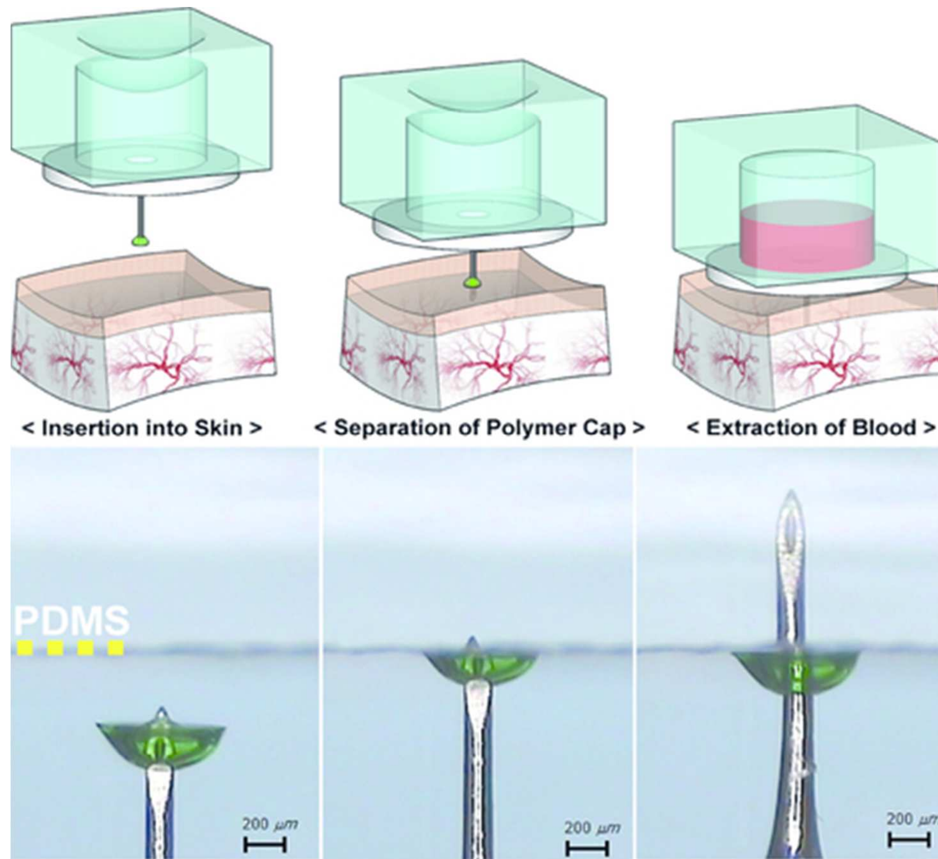

A self-powered one-touch blood extraction system is fabricated by the integration of a smart polymer-capped hollow microneedle and a pre-vacuum actuator. It is well suited for further integration with other microsystems (such as microfluidic chips, biosensors and electrode) to realize a real-time micro total analysis for point-of-care diagnosis.
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ARTICLE TYPE

Self-Powered One-Touch Blood Extraction System: Novel Polymer-Capped Hollow Microneedle Integrated with Pre-Vacuum Actuator

Cheng Guo Li, Manita Dangol, Chang Yeol Lee, Mingyu Jang and Hyungil Jung*

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Blood is the gold standard sample medium that can provide a wide variety of useful biological information for the diagnosis of various diseases. For portable point-of-care diagnosis, blood extraction systems have attracted attention as easier, safer, and more rapid methods of collecting small blood volumes. In this paper, we introduce a novel self-powered one-touch blood extraction system created by 10 assembling a smart polymer-capped hollow microneedle in a pre-vacuum polydimethylsiloxane actuator. The optimized hollow microneedle was precisely fabricated by drawing lithography for minimally invasive blood extraction, with a length of 1800 µm, an inner diameter of 60 µm, an outer diameter of 130 µm, and a 15° bevel angle. The system utilizes only a single step for operation; a finger press activates the blood sampling process based on the negative pressure-driven force built into the pre-vacuum activated 15 actuator. A sufficient volume of blood (31.3 ± 2.0 µl) was successfully extracted from a rabbit for evaluation by a micro total analysis system. The entire system was made of low-cost and disposable materials to achieve easy operation with a miniature structure and to meet the challenging requirements for single-use application in a point-of-care system without the use of any external power equipment.

Introduction

In recent years, much attention has been directed to micro total analysis systems (μTAS) using microfluidics as an easy, rapid, and sensitive method for point-of-care (POC) diagnosis.[1, 2] Because human whole blood is an important body fluid that can provide useful biological information for the diagnosis of various diseases, numerous portable analytical systems that use blood samples have been evaluated for applications in POC diagnosis.[3] With the miniaturization of analytical components in μTAS, even a tiny blood sample volume (less than tens of microliters) may be used for diagnosis. Most blood samples, however, are obtained using painful hypodermic needle puncture in the hospital or a self-administered finger prick at home, which requires a blood sampling system that is separate from the analytical components, an arrangement that may be inconvenient for patients.[4, 5] The application of microneedles and microactuators has allowed researchers to overcome this limitation and develop miniaturized blood extraction systems, which can easily be combined with micro analysis systems to achieve frameworks of complete real-time POC analysis.[6-9]

A number of solid and hollow microneedles have been designed and fabricated as alternatives to traditional hypodermic needle or finger prick blood sampling, and they provide a minimally invasive and less painful method by creating micro-scale pathways in the skin.[10-13] Also, many microactuators with different designs and operation methods such as electrostatic, piezoelectric, and magnetic approaches have been developed to provide power sources for blood extraction.[14, 15] Recently, several researchers have integrated the described microneedle and microactuator technology into μTAS as blood extraction systems.[16, 17] However, most of these systems require an external power source (usually a heater or a battery) resulting in a bulky structure and limitations to system miniaturization. To address this issue, a minimally invasive blood-extraction system using an elastic self-recovery actuator integrated with a hollow microneedle that had an ultra-high aspect ratio was developed.[18, 19] Although a novel pneumatic power-driven actuator was developed with no need for additional energy supply, the complicated fabrication method and multi-step operating process was not suitable for implementation in a μTAS.

To become a useful tool in a POC diagnostic system, an improvised miniature blood extraction system must include a reduction in the complexity of the actuator structure and a decreased number of external support instruments, such as heaters, batteries, or valves, while simultaneously simplifying the operation process. This will lead to lower manufacturing costs and enhanced user convenience. Polydimethylsiloxane (PDMS) has become one of the most popular biocompatible materials in the fabrication of microfluidic devices due to its attractive features of transparency, flexibility, gas permeability, and ease of fabrication with soft lithography.[20] In addition, the surface characteristics of PDMS can also be easily changed with plasma treatment to form the oxidized components Si–OH group for irreversible bonding with each other, and various PDMS-based functional microstructures have been developed by taking advantage of these features for μTAS.[21]

In this paper, we describe a novel self-powered one-touch blood extraction system that consists of a smart polymer-capped hollow microneedle and a pre-vacuum PDMS actuator. The polymer-capped hollow microneedle is used to maintain the pre-vacuumed system and to serve as a power switch that controls the initiation of the blood sampling process. In the pre-vacuum activation process, we manipulate the gas permeability characteristics of PDMS and parylene coating technology to induce a vacuum chamber, and then airproof the entire system with biocompatible parylene sealing to maintain the vacuum energy over a long period of time. This self-powered one-touch blood extraction system utilizes a simple one-step operation, which employs a finger press to activate the sampling process based on the negative pressure-driven force developed in the pre-vacuum actuator. This system achieves easy operation with a miniature structure and meets the challenging requirements for single-use application in POC diagnosis without the need for any external power supply.

Materials and methods

Fabrication of one-touch blood extraction system

The hollow microneedle with optimized structure for minimally invasive blood extraction was fabricated by a drawing lithography-based technique based on our previous work (see Supporting Information for the detailed fabrication method). The PDMS chamber was fabricated by pouring a 10:1 (v/v) prepolymer mixture of Sylgard 184 elastomer and curing agent (Dow Corning, USA) over the aluminum master (see Supporting Information, Fig. S1). The mixture was cured for one hour in an oven at 80 °C, and the resulting PDMS mold was carefully peeled away from the master and then assembled with the polymer-capped hollow microneedle in a concentric shaft to complete the one-touch blood extraction system. In total, three aluminum masters were used to fabricate different volumes of PDMS chambers. The height of the inside cylindrical chamber was 4 mm and the diameters were 3, 4, and 5 mm, respectively, resulting in three different volumes of PDMS chambers (28, 50, and 78 μl).

Polymer blocking hollow microneedle

Polymer Solution: In particular, the biocompatible polymers polyvinylpyrrolidone (PVP), carboxymethylcellulose (CMC), and sodium hyaluronate (HA) have been widely used as structural materials for the fabrication of coated and dissolving microneedles in medical applications.[22, 23] The optimal concentrations of PVP (36 kDa, Sigma, USA), CMC (90 kDa, low-viscosity, Sigma, USA) and HA (29 kDa, Soliance, France) have been used as matrix polymers to block the hollow structures of microneedle tips via dipping and capping methods. Green and red dyes (tartrazine, Bowon, Korea) containing viscous PVP solutions (35%, w/v) were prepared by dissolving PVP powder in green and red dye solutions (1%, w/v) at room temperature. Pink dye (tartrazine, Bowon, Korea) containing CMC solution (10%, w/v) and yellow dye (tartrazine, Bowon, Korea) containing HA solution (30%, w/v) were prepared by dissolving CMC and HA powders in pink and yellow dye solutions (1%, w/v), respectively. Dipping Method: The hollow microneedle was fixed in the downward direction on a micropositioner (syringe pump, New Era Pump Systems, USA), which was used to control the position and dipping rate. The microneedle was vertically dipped at a speed of 50 mm min^{-1} into the 100 μl polymer coating solution

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reservoir until the hollow structure of the microneedle tip was completely immersed in the solution. The withdrawal speed of the microneedle from the coating solution was manually maintained at 5 mm min^{-1} to produce a polymer film on the surface of the microneedle tip. Air-drying of the coated polymer was performed for 1 min immediately after the withdrawal step, and the dip-coating process was repeated until the required thickness of polymer coating was obtained.

Capping Method: A single polymer droplet was fabricated by a solution dispenser (ML-5000X, Musashi, Japan) and automated X, Y, and Z-stages (SHOT mini 100-s, Musashi, Japan) by discharging previously prepared polymer solutions onto the surface of a PDMS base layer at 0.9 kg f cm^{-1} for 0.05 s. The PDMS base layer with the dispensed polymer droplet was fixed in the downward direction on a micropositioner (syringe pump, New Era Pump Systems, USA) and was contacted with a microneedle, which was placed below the micropositioner. The sharp tip of the microneedle just passed through the center of the droplet and was inserted into PDMS base layer at a rate of 5 mm min^{-1}, and then was kept at room temperature for 4 min to solidify the polymer. Finally, an isolation step was performed to separate the polymer-capped microneedle from the PDMS base layer at a speed of 50 mm min^{-1}. The transparency property of the PDMS was used to control the tip position visually inside of the PDMS base layer.

Mechanical strength analysis

The mechanical force required for a polymer-blocked microneedle to penetrate into skin was measured by a displacement-force analyzer (Z0.5TN, Zwick, Germany) using 0.4-mm-thick synthetic skin, which simulated the high-resistance stratum corneum of human skin. The polymer-blocked microneedle was attached to the sensor probe of the force analyzer and pressed against the synthetic skin sheet at a speed of 60 μm s^{-1} via penetration force application. The axial fracture force measurement was performed by driving microneedles against an aluminum block at a rate of 60 μm s^{-1}. The maximum force before an immediate force drop was the penetration and fracture force for the microneedle tip. The force was recorded as a function of displacement associated with the microneedle.

Pre-vacuum within parylene treatment

Parylene-C dimer (Femto Science Co., Korea) is commonly used in a microprocessor-controlled parylene coating system (Femto Science Co., Korea). A parylene-C film with a thickness of 1 μm was thermally deposited on the surface of the closed one-touch blood extraction system by the following polymerization steps: (1) evaporation: parylene-C dimers (di-para-xylene) were first vaporized at a temperature of 160 ℃, (2) pyrolysis: the dimers were pyrolyzed at a temperature of 650 ℃ to form a highly reactive monomer (para-xylene) of parylene-C, and (3) deposition: the resulting polymer (poly-para-xylene) was finally coated onto the blood extraction system surface at room temperature. All of these processes were performed under vacuum conditions of less than 0.1 Torr in 1.5 hours. The thickness of the parylene-C film was controlled by setting a quartz crystal microbalance (QCM) in the deposition chamber, and the film thickness could be calculated by monitoring the frequency change in the QCM during deposition. The QCM change was measured from the beginning of the evaporation step, and the deposition was finished when the QCM frequency shift reached the value corresponding to the targeted thickness of the parylene-C film.

Characterization of surface properties

The surface morphologies of the pre-vacuum PDMS actuator with parylene coating were characterized by scanning electron microscopy (SEM; JEOL-7001, JEOL Ltd., Japan) at an accelerating voltage of 15 kV. All samples were coated with a thin layer of platinum using a sputtering machine for 100 s to produce a conductive surface prior to observation under SEM.

In vitro blood extraction

The liquid extraction capability of the one-touch blood extraction system was evaluated using distilled water (DW) and human whole blood samples treated with 8% (v/v) of the anticoagulant solution CPDA-1. Each system was attached to a pusher, which was connected to the micropositioner (syringe pump, New Era Pump Systems, USA) to allow accurate control of the insertion process for liquid extraction. The system was driven at a rate of 50 mm min^{-1} to insert the microneedle into the sample container with a synthetic skin cover to perform one-touch liquid extraction. After sampling, the system was removed from the sample container and the extraction volumes of the liquid samples were measured using a 100-μl syringe (Hamilton, USA).

In vivo blood extraction

A polymer-capped hollow microneedle with an inner diameter of 60 μm and a 15° bevel angle was integrated into the one-touch blood extraction system with 50 μl PDMS vacuum chamber. After fixing a rabbit (4 kg, New Zealand White) in a fixer, the blood extraction system, which was subjected to a vacuum in advance to induce the pressure-driven force to extract the blood sample, was pressed by a finger to induce the microneedle insertion into the ear artery of the rabbit. After the removal of the blood extraction system, the total extraction sample volume was measured with a 100-μl syringe (Hamilton, USA). The experiment was repeated in triplicate. All experimental procedures were approved by the Department of Laboratory Animal Medicine of the Yonsei University College of Medicine, and were performed in accordance with the Animal Research Committee Guidelines at the Yonsei University College of Medicine and approved by the AAALAC.

Results and discussion

Self-powered one-touch blood extraction system

As shown in Fig. 1a, the self-powered one-touch blood extraction system comprised three parts: 1) a vacuum PDMS chamber to provide the power for the blood extraction by pressure gradient-driven force and to store the extracted blood sample; 2) an optimized hollow microneedle to induce the micro-channel for minimally invasive blood sampling; and 3) a multi-functional polymer cap to block the hollow microneedle tip selectively and thus to maintain the closed pre-vacuum system, and to precisely control the initiation of the blood sampling process. The PDMS chamber was fabricated using a traditional micro-fabrication technique and was designed as an $8 \times 8 \times 5$ mm^3 cube, with a

cylindrical chamber having a 4-mm height and a 4-mm inside diameter (see Supporting Information, Fig. S1).[24, 25] The hollow microneedle with an inner diameter of 60 µm, an outer diameter of 130 µm, and a 15° bevel angle was fabricated by drawing lithography, and the use of this optimized microneedle structure for minimally invasive blood extraction had been demonstrated in our previous study, as shown in Fig. 1b.[26, 27]

The operating principle of this system is illustrated in Fig. 1c. One-touch contact with a finger inserted the microneedle into the skin, inducing the separation of the polymer cap from the microneedle tip under the resistance force of the skin barrier. Simultaneously, the blood sample was extracted into the PDMS chamber by the pressure gradient between the pre-vacuum chamber and the blood vessel. The polymer cap separation process was visualized using a transparent PDMS layer that simulated the skin barrier, as illustrated in Fig. 1d. Although the sharp microneedle tip could easily penetrate into the PDMS, the flat surface of the half sphere-shaped polymer cap resisted penetrating the PDMS leaving on the surface. This polymer cap separation simultaneously opened the blocked microneedle tip inside the PDMS layer and induced the blood sampling process.

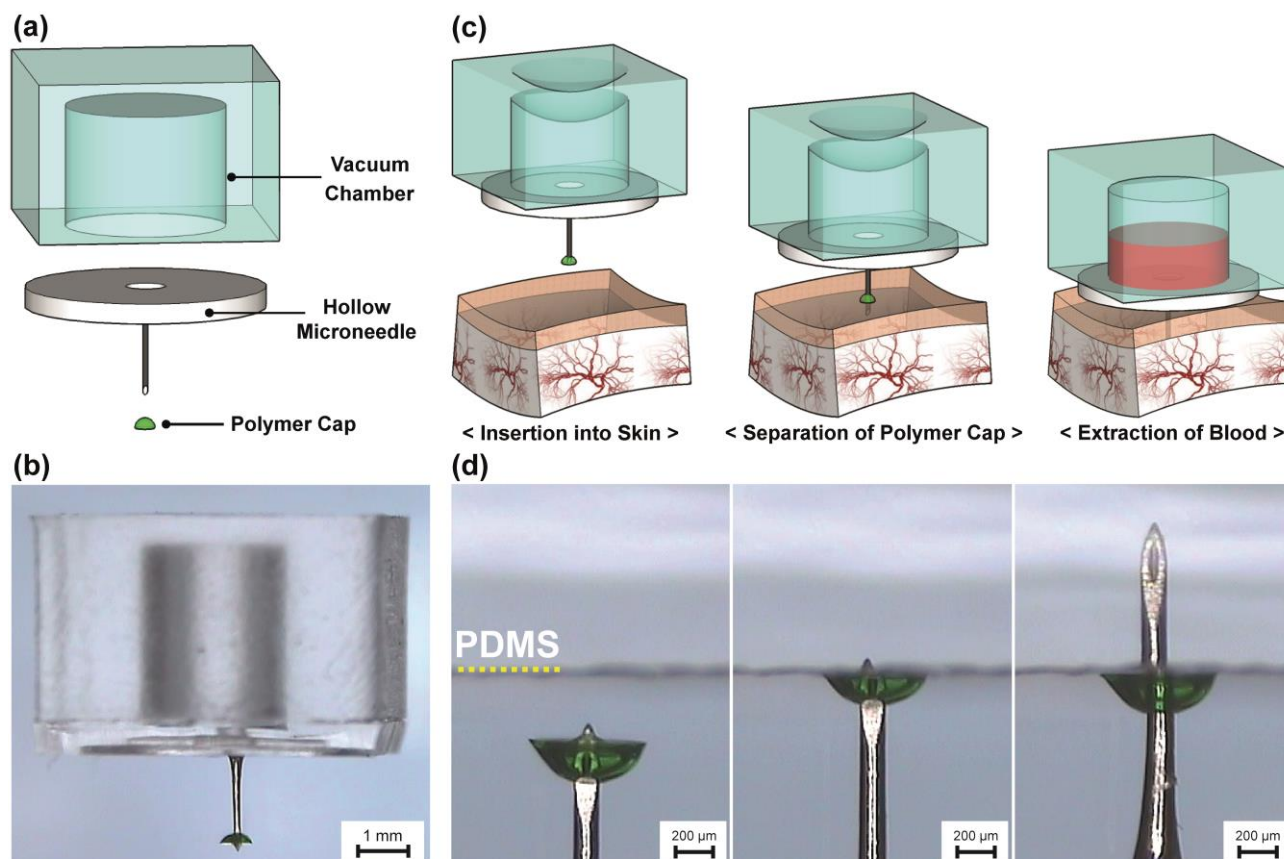

Fig. 1 Schematic representation of the self-powered one-touch blood extraction system. (a) Diagram of the blood extraction system, which integrated a vacuum chamber with the polymer-capped hollow microneedle (60 µm inner diameter, 130 µm outer diameter, and 15° bevel angle); (b) Image of the self-powered one-touch blood extraction system; (c) Operating principle for blood sampling: a one-touch press of the system induced the microneedle insertion into the skin with the polymer cap separation from the microneedle tip. Simultaneously, the blood sample was extracted into the chamber under the pressure gradient; (d) Separation process of the polymer cap from the microneedle tip.

Polymer-coated hollow microneedle

The hollow microneedle was blocked by being coated with viscous PVP (35%, w/v) solution with red dye using a micron-scale dipping method developed previously.[28, 29] As shown in Fig. 2a, the dipping method consisted of two distinct steps occurring in sequence: i) dipping the microneedle into the polymer solution to form a uniform polymer film on the microneedle tip and ii) withdrawal and drying to form a solid polymer coating on the microneedle tip. The thickness of the polymer coating was controlled by the number of dips; polymer coating thicknesses of 3.25 ± 0.44, 16.1 ± 2.09, 39.53 ± 1.93, and 78.6 ± 12.26 µm were obtained by dipping the microneedle into the polymer solution one, two, four, and six times, respectively (Fig. 2b). As expected, the thickness of the polymer coating on the microneedle tip increased as the number of dips increased. In penetration force analyses of the polymer-coated hollow microneedles, the coated polymer was found to insert into the synthetic skin together with the microneedle without leaving remnants on the surface (see inserts in Fig. 2c). Therefore, the penetration force of the polymer-coated microneedle increased noticeably from 0.56 ± 0.04 to 2.32 ± 0.23 N as the thickness of the polymer coating increased from 3.25 ± 0.44 to 78.6 ± 12.26 µm (Fig. 2c).

It is important to prepare a polymer-coated microneedle that not only blocks the hollow structure of the microneedle tip, but also minimizes penetration force. Although the increase in the number of dips increased the thickness of the polymer coating, resulting in a more secure blockage of the hollow microneedle, this also

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increased the penetration force due to the decreased sharpness of the microneedle. This suggests that this coating by the dipping method involves a trade-off between the blockage of the hollow microneedle and the diminished microneedle sharpness. That is, to ensure that the hollow of the microneedle is sufficiently blocked, at least four dips were required (data not shown); this coating, however, sacrificed the sharpness of the microneedle so that it required 2.36 times the original penetration force. In addition, more tissue deformation will be caused due to the increase in the outer diameter of the microneedle tip, which has been shown to be responsible for the pain caused by insertion into the skin.[30, 31]

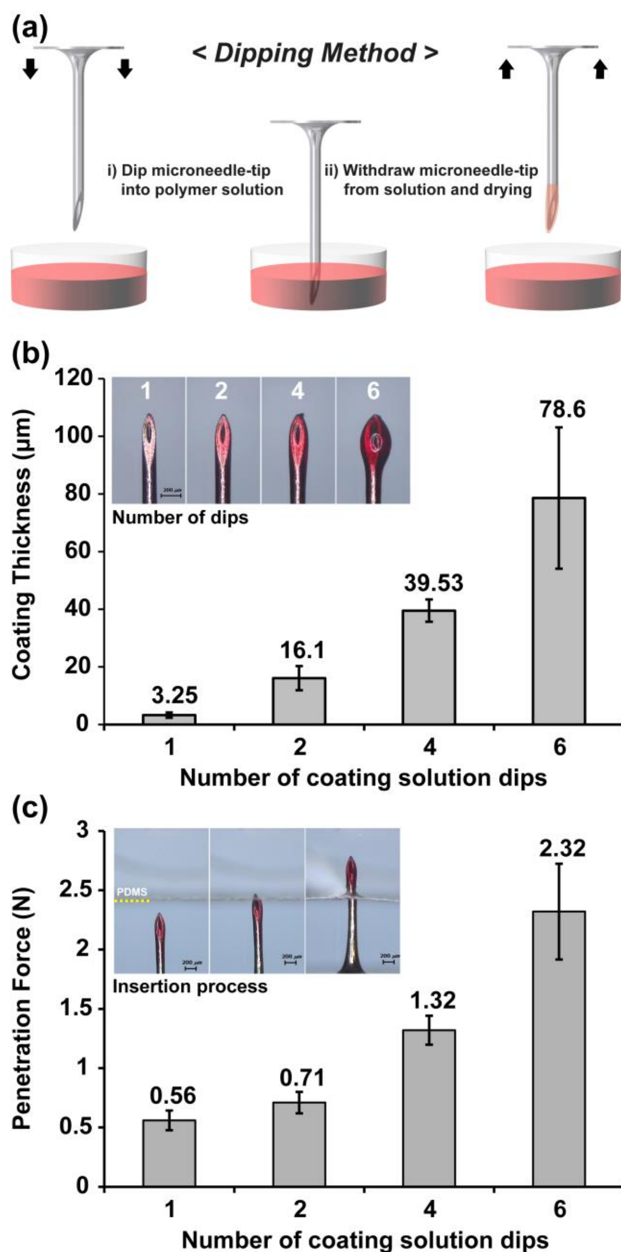

Fig. 2 (a) Schematic process for blocking the hollow structure of a microneedle by the dipping method; (b) Effect of the number of dips into the polymer solution on the coating polymer thickness; microscopy shows a uniform PVP polymer coating on the microneedle tip; (c) Penetration force measurements of polymer-coated microneedles, and microscope images of the insertion process. Measurement data are expressed as means ± standard deviations.

Polymer-capped hollow microneedle

The hollow microneedle was capped with viscous PVP (35%, w/v) polymer solution with green dye using a novel micron-scale capping method. As shown in Fig. 3a, this capping method consists of three steps: i) polymer dispensing on the surface of a PDMS base layer to form a single polymer droplet, ii) microneedle tip insertion into the polymer droplet, and iii) separation of the microneedle with the polymer cap from the PDMS base surface after drying.

In polymer dispensing, the determination of a sufficient droplet height to ensure the complete blockage of the hollow structure of the microneedle is critical (Fig. 3b). The height of the hollow in the microneedle was determined by inner diameter/(tan θ), where θ is the bevel angle of the microneedle. Also, we observed a decrease in the droplet height during the drying process. Thus, this drying process must be taken into account when selecting a droplet height that is sufficient to block the hollow completely. In the case of a microneedle with an inner diameter of 60 μm and a 15° bevel angle, the height of the hollow was 204 μm. When 0.144 μl of 35% (w/v) PVP polymer was dispensed onto the PDMS surface, the initial height of the resulting droplet was 409 μm and no additional decrease in height was observed after 4 min (about 250 μm) due to the complete evaporation of distilled water (see inserts in Fig. 3b). This implied that at least 0.144 μl of dispensed polymer droplet was required to produce a solid polymer cap with a height of 250 μm. Also, PDMS was used as the base layer because of its hydrophobicity, which enabled us to build up the droplet using a hydrophilic polymer solution and to separate the solid polymer cap easily from the base layer in the isolation step.

When we inserted the microneedle tip into the polymer droplet, the droplet with the PDMS base layer was fixed in the downward direction to precisely control contact with the microneedle tip. To cap the hollow structure, either an exposed tip or an embedded tip can be produced, as shown in Fig. 3c. The microneedle tip was passed through the droplet and driven continually to insert the sharp tip (the upper part of the hollow structure) into the soft PDMS base layer to form an exposed-tip capping structure. In contrast, for the embedded-tip capping structure, the tip of the microneedle was not inserted into the PDMS base layer.

The hollow microneedles with heights of 1800 μm, outer diameters of 130 μm, and bevel angles of 15° that were capped by polymer with exposed-tip and embedded-tip structures were used to analyze penetration force. Penetration force data was collected by driving microneedles into synthetic skin. As shown in Fig. 3d, the force increased with microneedle displacement and a sudden drop in force indicated the penetration of the synthetic skin by the microneedle. The average force required for skin penetration by microneedles without cap, with exposed-tip cap structures, and with embedded-tip cap structures were 0.49 ± 0.02, 1.31 ± 0.01, and 2.30 ± 0.10 N, respectively. In the case of the embedded tip, more penetration force was required because the microneedle tip penetrated into the skin after impaling the polymer cap. However, the microneedle tip is already exposed in the exposed-tip cap structure, thus minimizing the resistance from the polymer cap. The penetration force of the microneedles with the exposed-tip

caps (1.31 ± 0.01 N) was similar to that of the microneedles that were dipped four times into polymer solution (1.32 ± 0.07 N). However, the exposed-tip structure for polymer-capped hollow microneedles will reduce tissue injury due to the flat surface of the half sphere-shaped polymer cap left behind from insertion. As shown in Fig. S2, the viscous CMC (10%, w/v) and HA (30%, w/v) polymer solutions could also be used to form the exposed-tip polymer caps on the microneedles with the successful separation process.
Furthermore, successful blood extraction using microneedles with the exposed-tip caps requires the microneedle to have sufficient strength to penetrate skin without breakage. The average fracture force data (6.44 ± 0.28 N) collected by driving microneedles against an aluminum block are shown in Fig. S3. The safety ratio of the fracture (6.44 N) to penetration (1.31 N) force of the microneedle with the exposed-tip caps was 4.9. This proved that microneedle had sufficient mechanical strength compared to the penetration force for successful *in vivo* blood extraction without breakage.

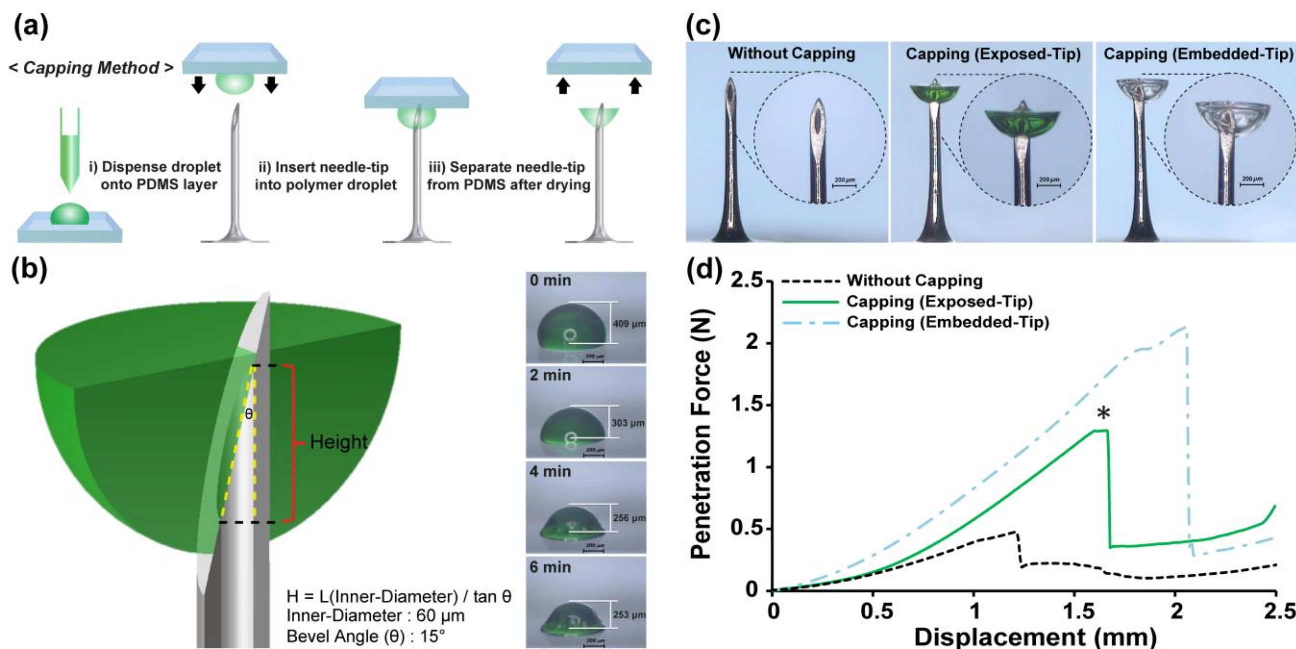

Fig. 3 (a) Schematic process for blocking the hollow structure of a microneedle by the capping method; (b) Tip structure of hollow microneedle with exposed-tip polymer cap, and the drying period of the polymer droplet on the surface PDMS base layer; (c) Images of hollow microneedles without a polymer cap, with an exposed-tip cap, and with an embedded-tip polymer cap; (d) A schematic illustration of the skin penetration force measurements of the polymer-capped microneedles (penetration was identified by a sudden drop in force).

Pre-vacuum activation

The high gas permeability property of PDMS was required to induce negative pressure by pre-vacuum activation for the closed one-touch blood extraction system. However, the gas leaking through the pores of PDMS made it difficult to maintain the applied negative pressure. Therefore, a parylene coating was used to seal the porous structure of the PDMS chamber effectively to address this issue; parylene is widely used as an inert coating material to enhance biomedical compatibility with low permeability to gases and moisture.[32, 33] All of the procedures for pre-vacuum activation and system airproofing were performed during the single parylene coating process.

After blocking the microneedle tip with the polymer, pre-vacuum activation was performed by maintaining low-pressure conditions for at least 20 min. Low-pressure conditions of less than 0.1 Torr can be achieved for 1.5 hours before parylene film deposition. Fig. 4a shows the pre-vacuum activation and parylene film deposition process schematically. The air was evacuated through the porous structure of PDMS to form negative pressure inside the PDMS chamber. Then, parylene was deposited on the surface of the PDMS to seal the porous structure with parylene caulk inside and with film outside.[34] Fig. 4b and c present the scanning electron microscope (SEM) images of the PDMS chamber surface before and after the deposition of a 1-μm-thickness parylene film coating. This potential energy, which was stored inside the one-touch blood extraction system, provided the driving force for blood sampling when interconnected with a blood vessel via the channel of the hollow microneedle. The pre-vacuum activation mechanism demonstrated that this system can be used for blood sampling without the need of an external power source. Furthermore, the parylene film deposition was verified to maintain the pre-vacuum activation of blood extraction system for more than 10 hours (data not shown), which was also confirmed by Satoshi Konishi group.[34] For the future mass production and commercialization, a vacuum sealed packing (such as vacuum pouch or container) could be used to keep the system activated and ensure the long term storage conditions (a few months or even years) for clinical applications.

As shown in fabrication method of hollow microneedle (see Supporting Information), the preferred metal for microneedle fabrication was nickel due to high strength and economical value. However, the biocompatibility issues of nickel hollow microneedle may become a hurdle for biomedical applications. Thus, during the single parylene coating process 1 μm thick

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parylene layer was simultaneously coated onto the surface of microneedle to enhance the biomedical compatibility, thus increasing the potential for clinical applications.[35] Moreover, it can be an interesting subject of research to find economical and biocompatible material alternative to nickel.

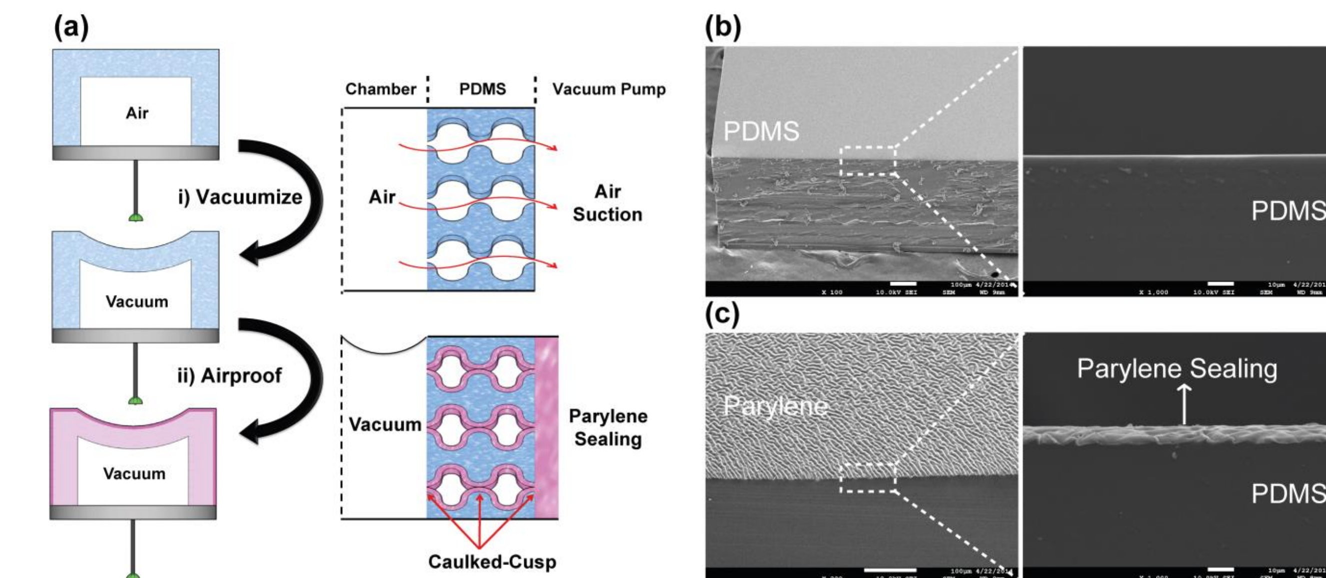

Fig. 4 Schematic diagram of the pre-vacuum activation and parylene coating process for the one-touch blood extraction system. (a) A cross-sectional illustration of the pre-vacuum activation and airproofing of the blood extraction system. The closed system was placed inside the vacuum container of the parylene coating system: i) vacuumize: the air inside of the closed system was evacuated through the porous structure of PDMS to form a vacuum chamber; ii) airproof: a parylene film was coated onto the surface, sealing the porous structure of PDMS to form a hermetic pre-vacuum system. Scanning electron microscopy images of the PDMS chamber surface (b) before and (c) after parylene film deposition.

Performance characteristics in blood extraction

In polymer-coated hollow microneedles prepared by the dipping method, the complete dissolution of the coated polymer on the microneedle tip was required to induce liquid extraction. As shown in Fig. 5a, sample extraction was initiated after 120 seconds when a polymer-coated hollow microneedle was inserted into a sample container (see Supporting Information Video 1). Because the exposed-tip polymer-capped microneedle required less penetration force than the embedded-tip microneedle did, we tested the blood extraction performance of the exposed-tip microneedle, which showed an immediate initiation of liquid extraction, completing the process in 4 seconds, as shown in Fig. 5b (see Supporting Information Video 2). The delayed initiation of the blood extraction was observed only in the polymer-coated method, which required the full dissolution of the coated polymer; no such dissolution was required for microneedles with the polymer caps, which were left behind during insertion. Blood collection was completed in 4 seconds after the initiation of blood extraction for both the polymer-coated and polymer-capped methods. Because less tissue injury was induced by the polymer-capped method, which polymer cap left behind without insertion into skin with microneedle, and as the rapid-response blood extraction was more suitable for a one-touch system to be applied in a POC system, the exposed-tip polymer-capped hollow microneedles were used in the experiments that followed.

The extracted sample volume depends on the volume of the vacuum chamber. Thus, the PDMS chamber was modified by varying the diameter of the inside cylindrical chamber to be 3, 4, or 5 mm while maintaining the height of the chamber at 4 mm. We measured the extraction volumes of red-dyed distilled water and human whole blood samples for the PDMS vacuum chambers with three different volumes of about 28, 50, and 78 µl. As shown in Fig. 5c, the extraction volumes of these two materials increased according to volumes of the vacuum PDMS chambers. Less volume was extracted for the whole blood sample compared to the distilled water sample even for the same chamber volume; this may be explained by differences in viscosity, because the pressure loss by pipe friction increases as viscosity increases.[36] The liquid extraction results indicate that it was possible to control the extracted sample volume of this system by restructuring the PDMS vacuum chamber.

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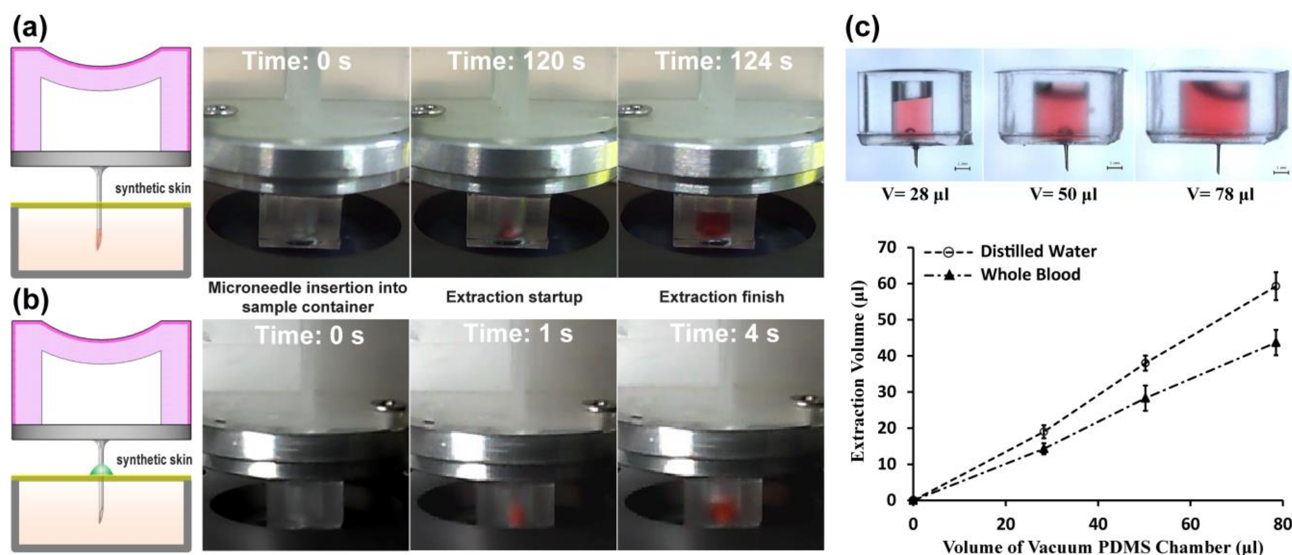

Fig. 5 *In vitro* liquid extraction test of one-touch blood extraction system. Force was applied to the one-touch blood extraction system to induce the microneedle insertion into a sample container to perform liquid extraction. (a) Representative results of the delayed liquid extraction process by a polymer-coated hollow microneedle; (b) Representative results of the rapid-response liquid extraction process by an exposed-tip polymer-capped hollow microneedle; (c) Distilled water (○, n = 3) and whole blood (▲, n = 3) extraction by the one-touch blood extraction system with an exposed-tip polymer-capped hollow microneedle (60 µm inner diameter) using various volumes of PDMS vacuum chambers (28, 50 and 78 µl). Extraction measurement data are expressed as means ± standard deviations.

In vivo blood extraction

The *in vivo* blood extraction of this self-powered one-touch system was performed on a live rabbit (New Zealand White, DooYeol Biotech, Korea) using exposed-tip polymer-capped hollow microneedle with an inner diameter of 60 µm. All the blood extraction experiments were repeated three times and no broken or crooked microneedle was observed (data not shown). A pre-vacuum activated system with a PDMS chamber having a 50-µl volume was used to extract 31.3 ± 2.0 µl of blood sample without bubbles formation in 4 seconds by deploying the microneedle into the ear artery of the rabbit (Fig. 6a and Supporting Information Video 3). In contrast, blood sampling was not possible without a pre-vacuum system, implying that this system of inducing negative pressure is critical to the extraction of a sufficient blood sample for a micro-analysis system (>5 µl).[37] The pre-vacuum activated system extracted 31.3 ± 2.0 µl of blood, yielding a sufficient volume for further use in a micro-analysis system (Fig. 6b). However, the hemolysis or protein loss of blood sample could be a hurdle for biomedical applications. Thus, our future research is to develop one-touch analysis system by integrating this system with biosensor chip, and confirm if any vital signals loss occurs in blood following extraction. A coating of biocompatible materials onto the inner surface of hollow microneedle or PDMS chamber may solve the biocompatibility issues, so that it can be potentially connected to other analytical devices, such as an electrode sensor, pad sensor, or microfluidic chip for clinical applications.

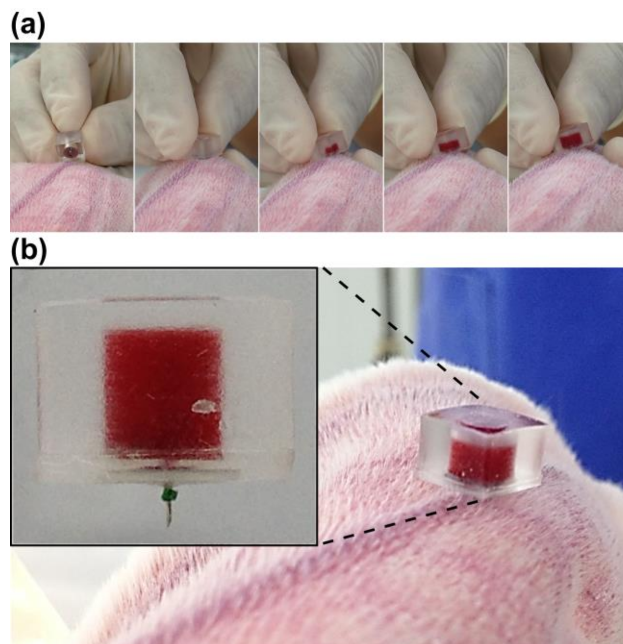

Fig. 6 *In vivo* blood extraction by the self-powered one-touch blood-extraction system. (a) Application of the blood extraction system in a rabbit ear artery by a one-touch finger press, which extracted a blood sample into a PDMS vacuum chamber with a 50-µl volume using a microneedle with an inner diameter of 60 µm. (b) The extracted blood sample in the system's chamber with the polymer cap separated from the microneedle tip.

Conclusions

In summary, we have designed and fabricated a novel self-powered one-touch blood-extraction system by integrating a smart polymer-capped hollow microneedle and pre-vacuum actuator. This disposable one-touch system based on the negative pressure-driven force developed in the pre-vacuum actuator with no need for additional electrical power source. The blood sample volumes extracted via this one-touch system were determined by the pre-vacuum PDMS chamber volumes, and successful *in vivo* blood sampling was demonstrated in a rabbit experiment. The self-powered mechanism, disposability, and simplicity of one-touch operation make this system well-suited for further integration with other microsystems, such as microfluidic chips,[38, 39] biosensors,[40, 41] and electrode sensors,[42, 43] which may be used to realize a real-time micro total analysis system for POC diagnosis.

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Notes and references

Department of Biotechnology, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul, Korea. Fax: +82-2-362-7265; Tel: +82-2-2123-7418; E-mail: hijung@yonsei.ac.kr

† Electronic Supplementary Information (ESI) available: Videos of delayed water extraction, rapid-response water extraction, pre-vacuum activated system for *in vivo* blood extraction, pre-vacuum inactivated system for *in vivo* blood extraction. See DOI: 10.1039/b000000x/

1. L. Gervais, N. De Rooij and E. Delamarche, *Adv. Mater.*, 2011, **23**, H151-H176.
2. A. K. Yetisen, M. S. Akram and C. R. Lowe, *Lab Chip*, 2013, **13**, 2210-2251.
3. M. Toner and D. Irimia, *Annu. Rev. Biomed. Eng.*, 2005, **7**, 77.
4. A. Windich-Biermeier, I. Sjoberg, J. C. Dale, D. Eshelman and C. E. Guzzetta, *J. Pediatr. Oncol. Nurs.*, 2007, **24**, 8-19.
5. R. J. Kuriger and B. F. Romanowicz.
6. A. Oki, M. Takai, H. Ogawa, Y. Takamura, T. Fukasawa, J. Kikuchi, Y. Ito, T. Ichiki and Y. Horiike, *Jpn. J. Appl. Phys.*, 2003, **42**, 3722.
7. G. E. Gattiker, K. V. Kaler and M. P. Mintchev, *Microsyst. Technol.*, 2005, **12**, 44-51.
8. T. Li, A. Barnett, K. L. Rogers and Y. B. Gianchandani, *Lab Chip*, 2009, **9**, 3495-3503.
9. A. V. Ganesan, H. Kumar, S. Swaminathan, K. Singh, R. A. Joy, N. Sood, T. Gokhale and R. Mittal, *Bionanoscience*, 2014, **4**, 128-135.
10. H. J. Gardeniers, R. Luttge, E. J. Berenschot, M. J. De Boer, S. Y. Yeshurun, M. Hefetz, R. van't Oever and A. van den Berg, *J. Microelectromech. Syst.*, 2003, **12**, 855-862.
11. P. Zhang, C. Dalton and G. A. Jullien, *Microsyst. Technol.*, 2009, **15**, 1073-1082.
12. B. P. Chaudhri, F. Ceyssens, P. De Moor, C. Van Hoof and R. Puers, *J. Micromech. Microeng.*, 2010, **20**, 064006.
13. K. Tsuchiya, S. Jinnin, H. Yamamoto, Y. Uetsuji and E. Nakamachi, *Precis. Eng.*, 2010, **34**, 461-466.
14. A. Nisar, N. Afzulpurkar, B. Mahaisavariya and A. Tuantranont, *Sens. Actuator B-Chem.*, 2008, **130**, 917-942.
15. M. W. Ashraf, S. Tayyaba and N. Afzulpurkar, *Int. J. Mol. Sci.*, 2011, **12**, 3648-3704.
16. G. Liu, C. Shen, Z. Yang, X. Cai and H. Zhang, *Sens. Actuator A-Phys.*, 2010, **163**, 291-296.
17. A. Al-Halhouli, M. Kilani and S. Büttgenbach, *Sens. Actuator A-Phys.*, 2010, **162**, 172-176.
18. C. G. Li, K. Lee, C. Y. Lee, M. Dangol and H. Jung, *Adv. Mater.*, 2012, **24**, 4583-4586.
19. S. Park, S. H. Um and Y.-K. Kim, *BioChip J.*, 2012, **6**, 372-378.
20. M. Zhang, J. Wu, L. Wang, K. Xiao and W. Wen, *Lab Chip*, 2010, **10**, 1199-1203.
21. G. S. Fiorini and D. T. Chiu, *BioTechniques*, 2005, **38**, 429-446.
22. Y.-C. Kim, J.-H. Park and M. R. Prausnitz, *Adv. Drug Del. Rev.*, 2012, **64**, 1547-1568.
23. J. D. Kim, M. Kim, H. Yang, K. Lee and H. Jung, *J. Controlled Release*, 2013, **170**, 430-436.
24. B.-H. Jo, L. M. Van Lerberghe, K. M. Motsegood and D. J. Beebe, *J. Microelectromech. Syst.*, 2000, **9**, 76-81.
25. N. L. Jeon, D. T. Chiu, C. J. Wargo, H. Wu, I. S. Choi, J. R. Anderson and G. M. Whitesides, *Biomed. Microdevices*, 2002, **4**, 117-121.
26. K. Lee, H. C. Lee, D. S. Lee and H. Jung, *Adv. Mater.*, 2010, **22**, 483-486.
27. C. G. Li, C. Y. Lee, K. Lee and H. Jung, *Biomed. Microdevices*, 2013, **15**, 17-25.
28. H. S. Gill and M. R. Prausnitz, *J. Controlled Release*, 2007, **117**, 227-237.
29. H. S. Gill and M. R. Prausnitz, *Pharm. Res.*, 2007, **24**, 1369-1380.
30. K. Tsuchiya, K. Isobata, M. Sato, Y. Uetsuji, E. Nakamachi, K. Kajiwara and M. Kimura, Design of painless microneedle for blood extraction system, 2007.
31. H. S. Gill, D. D. Denson, B. A. Burris and M. R. Prausnitz, *Clin. J. Pain*, 2008, **24**, 585.
32. T. Y. Chang, V. G. Yadav, S. De Leo, A. Mohedas, B. Rajalingam, C.-L. Chen, S. Selvarasah, M. R. Dokmeci and A. Khademhosseini, *Langmuir*, 2007, **23**, 11718-11725.
33. G.-Y. Lee, Y.-H. Choi, H.-W. Chung, H. Ko, S. Cho and J.-C. Pyun, *Biosens. Bioelectron.*, 2013, **40**, 227-232.
34. S. Sawano, K. Naka, A. Werber, H. Zappe and S. Konishi, Sealing method of PDMS as elastic material for MEMS, 2008.
35. J. Oh, K. Liu, T. Medina, F. Kralick and H. M. Noh, *Microsyst. Technol.*, 2014, **20**, 1169-1179.
36. K. Tsuchiya, N. Nakanishi, Y. Uetsuji and E. Nakamachi, *Biomed. Microdevices*, 2005, **7**, 347-353.
37. I. K. Dimov, L. Basabe-Desmonts, J. L. Garcia-Cordero, B. M. Ross, A. J. Ricco and L. P. Lee, *Lab Chip*, 2011, **11**, 845-850.
38. D. Yang, X. Niu, Y. Liu, Y. Wang, X. Gu, L. Song, R. Zhao, L. Ma, Y. Shao and X. Jiang, *Adv. Mater.*, 2008, **20**, 4770-4775.
39. B. Yuan, Y. Li, D. Wang, Y. Xie, Y. Liu, L. Cui, F. Tu, H. Li, H. Ji and W. Zhang, *Adv. Funct. Mater.*, 2010, **20**, 3715-3720.
40. M.-I. Mohammed and M. P. Desmulliez, *Lab Chip*, 2011, **11**, 569-595.
41. J. C. Claussen, A. Kumar, D. B. Jaroch, M. H. Khawaja, A. B. Hibbard, D. M. Porterfield and T. S. Fisher, *Adv. Funct. Mater.*, 2012, **22**, 3399-3405.
42. H. Tang, F. Yan, P. Lin, J. Xu and H. L. Chan, *Adv. Funct. Mater.*, 2011, **21**, 2264-2272.
43. G. Dutta, S. Kim, S. Park and H. Yang, *Anal. Chem.*, 2014.