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Low-cost fabrication of poly(methyl methacrylate) microchips using disposable gelatin gel templates

Zhi Chen [a], Zhengyin Yu [b], Gang Chen [a,*]

[a] School of Pharmacy, Fudan University, Shanghai 200032, China
[b] Shanghai Institute of Microsystem and Information Technology, Shanghai 200050, China

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ABSTRACT

A simple method based on disposable gelatin gel templates has been developed for the low-cost fabrication of poly(methyl methacrylate) (PMMA) microfluidic chips. Gelatin was dissolved in glycerol aqueous solution under heat to prepare a thermally reversible impression material. The molten gel was then sandwiched between a glass plate and a SU-8 template bearing negative relief of microstructure. After cooling, the negative SU-8 template could be easily separated from the solidified gelatin gel and a layer of gelatin template bearing positive relief of the microstructure was left on the glass plate. Subsequently, prepolymerized methyl methacrylate molding solution containing a UV-initiator was sandwiched between the gel template and a PMMA plate and was allowed to polymerize under UV light to fabricate PMMA channel plate at room temperature. Complete microchips could be obtained by bonding the channel plates with covers using plasticizer-assisted thermal bonding at 90 °C. Gelatin gel template can be mass-produced and will find application in the mass production of PMMA microchips at low cost. The prepared microfluidic microchips have been successfully employed in the capillary electrophoresis analysis of several ions in connection with contactless conductivity detection.

1. Introduction

Since the pioneering work of Manz and Harrison, more and more research attentions have been paid to microfluidic chips owing to their high degree of integration, portability, minimal reagent consumption, high performance and speed [1,2]. Most early reports on microfluidic chips relied on glass or silicon substrates in combination with standard lithographic fabrication technology. However, their application was limited because of high cost, harmful and complicated fabrication procedures, and the limitation on the mass production [3]. Polymers are less expensive and easier to be manipulated than glass-based substrates and are becoming the most promising materials for fabricating microfluidic devices with mass-replication technologies, such as injection molding and hot embossing [4,5].

PMMA is one of the most commonly used polymers in microfluidics [6,7]. It is particularly useful for microfluidic chips with the features of attractive chemical properties, low price, excellent optic transparency, ease of fabrication, biocompatibility, and excellent electric and mechanical properties [8–10]. Because PMMA can decompose into methyl methacrylate (MMA) at a high temperature and can be reused, it is an ideal material for preparing "green microchips". In addition, its unique chemical and physical properties offer great promise for the fabrication of microdevices with useful functionalities.

A variety of approaches have been developed for the fabrication of PMMA microfluidic chips, including laser ablation [8], imprinting [10], injection molding [11], *etc.* Recently, methods based on the in situ polymerization of MMA in molds were developed for the fabrication of PMMA microchips with the aids of ultraviolet (UV) light [12] and heat [13]. One bottleneck of these molding methods was the long polymerization time in the range of 4–12 h that are incompatible with the mass production of microfluidic chips. More recently, a method based on in situ surface polymerization was developed for the rapid fabrication of PMMA microchips [14]. The images of the raised microchannels on a nickel template were precisely replicated into the PMMA substrates during the UV-initiated polymerization of the MMA prepolymer molding solution within 30 min under ambient temperature. To date, the commonly used templates for molding PMMA microchips were made from silicon or metals using photolithography and wet-etching [6]. However, the silicon template is fragile and readily tends to be broken during molding process while the fabrication procedures of metal templates are expensive and time-consuming. In addition, the bonding between the molded PMMA channel plates

* Corresponding author at: School of Pharmacy, Fudan University, 826 Zhangheng Road, Shanghai 201203, China. Tel.: +86 21 5198 0061; fax: +86 21 6564 1740.
E-mail address: gangchen@fudan.edu.cn (G. Chen).

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and the templates was usually very strong and resulted in difficult demolding. It is a challenging work to develop simple approaches to fabricate easy releasing templates using inexpensive materials. We have fabricated poly(dimethylsiloxane) (PDMS) templates by soft lithography to produce PMMA microchips by in situ surface polymerization [15]. However, PDMS templates needed to be pretreated at 150 °C for 6 h to minimize the swelling during the polymerization of the molding solution. Gelatin is a translucent, colorless, odorless, brittle, nearly tasteless solid substance and is made from the collagen inside animals' skin and bones [16]. It has found wide applications in the fields of biomedicine, daily chemicals, food industry, *etc*. It is commonly used as a gelling agent in food, pharmaceuticals, photography, and cosmetic manufacturing. Gelatin constitutes the shells of pharmaceutical capsules in order to make them easier to swallow [17]. It can be plasticized by water and glycerol to form gelatin gel that has been widely applied to prepare the shells of soft capsules. Gelatin gel is a thermally reversible gel with low melting point and high strength and elasticity [17]. It is a promising impression material to fabricate disposable templates for the mass production of PMMA microchips at low cost.

In this work, a novel method based on disposable gelatin gel templates was developed for the mass production of PMMA microfluidic chips at low cost. Molten gelatin gel was cast on a SU-8 template bearing negative relief of channel network to prepare a disposable gel template. Subsequently, prepolymerized MMA molding solution was allowed to cure between the gelatin template and a PMMA plate under UV light at room temperature to prepare PMMA channel plates. Complete microchips could be obtained by bonding the channel plates with covers at 90 °C with the aid of a plasticizer. The ease, simplicity, versatility, and low cost of the novel fabrication approach thus make it extremely attractive for the mass production of PMMA microfluidic chips. The feasibility and performance of the obtained microchip have been demonstrated by separating and detecting ionic species in connection with contactless conductivity detection (CCD).

2. Experimental

2.1. Reagents

Methyl methacrylate (MMA), benzoin ethyl ether (BEE), 2-2′-azo-bis-isobutyronitrile (AIBN), dibutyl phthalate (DBP), glycerol, and gelatin were purchased from SinoPharm (Shanghai, China). Prior to use, the MMA need to be washed with 5% NaOH aqueous solution to remove the inhibitor and distilled under vacuum. AIBN was purified by recrystallization using hot methanol. Other reagents were all analytical grade. SU-8 50 photoresist and XP SU-8 developer were obtained from MicroChem (Newton, MA, USA). The running buffer for the microchip electrophoresis was a mixture solution containing boric acid and tris(hydroxymethyl)aminomethane (20 mM each, pH 8.0).

2.2. Fabrication of negative SU-8 template

Simple-cross microfluidic chip (75 mm × 16 mm) was designed and fabricated in this work. Photolithographic positive mask designed using a software (Adobe Illustrator CS3, Adobe) was transferred onto a transparency film at a local photo shop using a high-resolution printer at a resolution of 3600 dpi. It consisted of a 65 mm long separation channel and a 10 mm long injection channel that crossed each other at the middle point of the injection channel while the distance between one end of the separation channel and the injection cross was 5 mm. The channel network was represented by 50 μm wide black lines on a transparent background. The SU-8 50 negative photoresist was coated on a 4-in. silicon wafer using a spin-coater (KW-4A, Micro-electronics Research Center, Chinese Academy of Sciences, Beijing, China) at 2500 rpm for 50 s. The wafer bearing the photoresist layer was prebaked at 65 and 95 °C, with hold times of 5 and 15 min, respectively. Subsequently, the mask was placed on the photoresist-coated silicon wafer and exposed to UV light (365 nm) at a dose of ~300 mJ/cm^2. After exposure, the wafer was postbaked with hold times of 2 and 4 min at 65 and 95 °C, respectively. Finally, the wafer was developed using XP SU-8 developer for 6 min and was cleaned using the spin-coater at 1000 rpm for 100 s to obtain the negative SU-8 template.

2.3. Melting replication of positive gelatin template

To prepare thermally reversible gelatin impression material, 10 g gelatin was allowed to swell in a mixture solution of 12 g water and 6 g glycerol at room temperature for 6 h and then dissolved at 75 °C for 3 h. Prior to use, the obtained gelatin gel was melted in a 75 °C water bath. As illustrated in Fig. 1, about 1.5 mL of the gelatin solution (Fig. 1a) was cast on the negative SU-8 template (Fig. 1d) that consisted of a layer SU-8 layer bearing negative relief of the microstructure (Fig. 1b) and a silicon wafer (Fig. 1c). A piece of ground glass plate (76.2 mm × 25.4 mm × 1.2 mm, Fig. 1e) was then pressed on it slightly so that a layer of gelatin solution formed between the negative SU-8 template and the glass plate. Note that all these procedures were operated in a 40 °C chamber to prevent the gelation of the gelatin solution. Subsequently, the device was taken out and allowed to stand at 5 °C for 10 min (Fig. 1C), the gelatin solution gelated to form a layer of gel template (Fig. 1f). The thickness of the gelatin template was defined to be ~0.5 mm by using a spacer sandwiched between the glass plate and the SU-8 negative template. Finally, the negative SU-8 template was separated from the gelatin layer to obtain a soft gel template that strongly adhered on the ground glass plate.

2.4. Fabrication of PMMA microchip using gelatin gel template

MMA containing BEE (0.2% w/v, a UV-initiator) and AIBN (0.2% w/v, a thermal initiator) was allowed to prepolymerize in an 85 °C water bath for ~15 min to generate a dense prepolymer molding solution. The molding solution can further polymerize under heat or UV light and should be stored in a dark refrigerator at 4 °C. To prepare the PMMA channel plate, about 1.5 mL of the molding solution (Fig. 1g) was directly cast on a gelatin template (Fig. 1f) along its midline from one side to another side. Subsequently, a PMMA plate (75 mm × 16 mm × 1 mm, Fig. 1h) was covered on it and pressed slightly until that all the interspaces were filled by the molding solution. After the sandwiched molding solution was exposed to UV light (Fig. 1i) at 25 °C for 30 min to polymerize completely, the obtained channel plate (Fig. 1j) could be easily separated from the gelatin gel template. The cover sheet (~80 μm-thick, Fig. 1k) was fabricated in the same way as the PMMA channel plate except the template was replaced by a glass plate (76.2 mm × 25.4 mm × 1.2 mm).

Prior to sealing, 2-mm-diameter access holes (Fig. 2f) were drilled at the ends of the open channels (Fig. 2g and h) on the channel plate (5 mm × 16 mm × 1.3 mm, Fig. 2i) to create reservoir ports. The channel plate (Fig. 2i) and the cover (75 mm × 16 mm × 80 μm; area, 12 cm^2, Fig. 2a) were cleaned by sonicating in water and isopropanol for 1 min each and were dried under a stream of compressed air. Subsequently, the PMMA cover (Fig. 2a) was covered on a piece of PMMA plate (77 mm × 25 mm × 1 mm, Fig. 2b). An accurate amount (60 μL, i.e. 5 μL/cm^2 cover) of 5% (w/v) DBP solution in isopropanol (Fig. 2d) was applied to the interspaces between them via a microliter syringe (Fig. 2c). The bonding solution spread very fast to form a liquid film between them. And then, the cover (Fig. 2a)

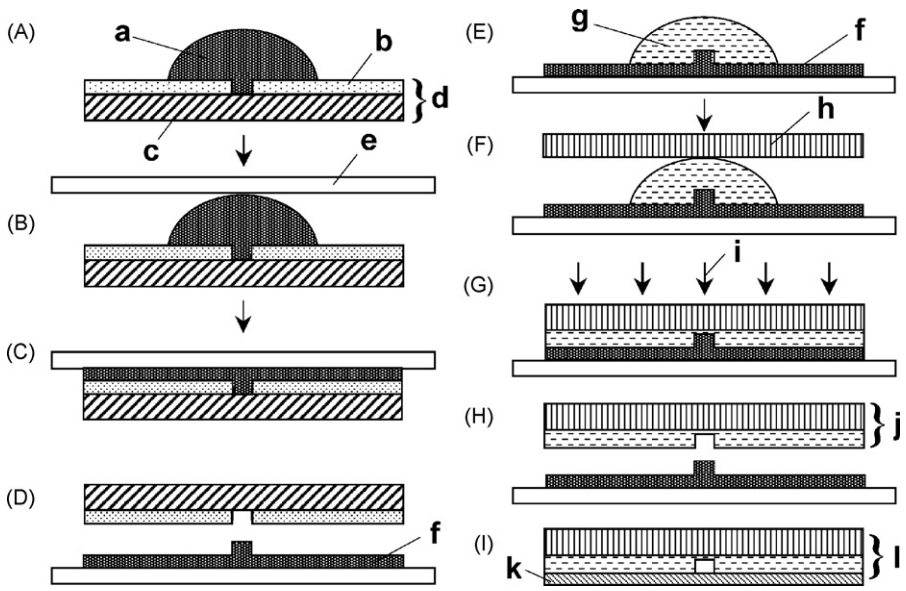

Fig. 1. Schematic showing the fabrication procedures of gelatin gel template (A–D) and PMMA microfluidic chip (E–I). (a) Molten gelatin gel, (b) patterned SU-8 layer, (c) silicon wafer, (d) negative SU-8 template bearing open channel network, (e) ground glass plate, (f) gelatin gel template, (g) prepolymerized MMA molding solution, (h) PMMA plate, (i) UV light, (j) PMMA channel plate, (k) PMMA cover, and (l) complete PMMA microchip.

was pulled away in the parallel direction to the PMMA plate (Fig. 2b) and the coating on the cover was exposed in the air for at least 2 min at room temperature, allowing isopropanol to evaporate. Finally, the cover (Fig. 2a) and the channel plate (Fig. 2i) were aligned with the coated surface of the cover and the channel-bearing surface of the channel plate touched face-to-face and sandwiched between two glass slides (76.2 mm × 25.4 mm × 1.2 mm, Fig. 2e). After they were clamped together between the upper and lower indenters of a laboratory-built hot press, a pressure of 0.6 MPa (Fig. 2j) was applied on them at 90 °C for 10 min. The bonded chip (Fig. 2n) was then allowed to cool slowly to room temperature and was removed from the glass slides (Fig. 2e). Fig. 1l illustrates the schematic of the cross section of a PMMA microchip.

2.5. Apparatus

Scanning electron microscopy (SEM) images of the channels in the PMMA microchips were obtained using a Philips XL 30 scanning electron microscope (Netherlands). The microchip electrophoresis-contactless conductivity detection (CCD) system used in this work has been described previously [18–20]. It consisted of a homemade +3000 V high-voltage dc power supply, a contactless conductivity detector linked with movable CCD electrode pairs, and a simple-cross PMMA microchip. A VC 2002 function generator (Victor Electronics, Shenzhen, China) was used to generate a sinusoidal signal (frequency, 400 kHz; peak-to-peak amplitude, 5 V) that was applied to the CCD electrode pairs on the cover of the PMMA

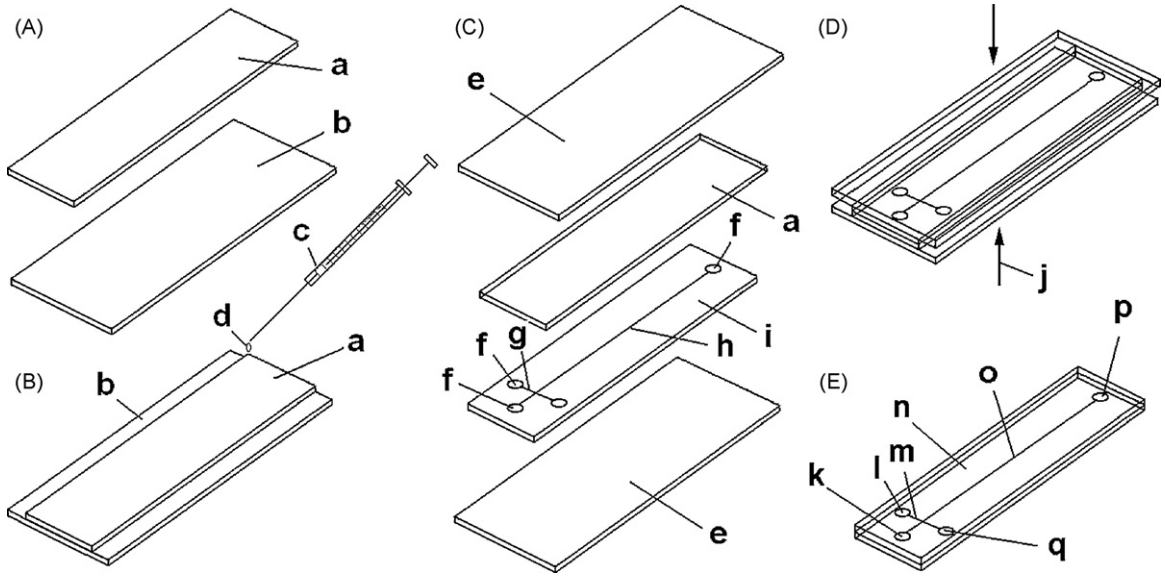

Fig. 2. Schematic showing the bonding process of a PMMA microchip. (A) Covering a PMMA cover (a) on a piece of PMMA plate (b); (B) applying an accurate amount of DBP solution in isopropanol (d) between (a) and (b) using a syringe (c); (C) exposing the coated surface of (a) in air to allow isopropanol to evaporate and sandwiching (a) and a channel plate (i) between two microscope slides (e) served as upper and lower pressure pads; (D) bonding (a) and (i) between two microscope slides (e) under pressure (j) at 90 °C for 10 min; (E) removing the complete microchip (n) from the bonding device. (f) Hole on (i); (g) open injection channel; (h) open separation channel; (k) running buffer reservoir; (l) sample reservoir; (m) injection channel; (o) separation channel; (p) outlet reservoir; (q) unused reservoir.

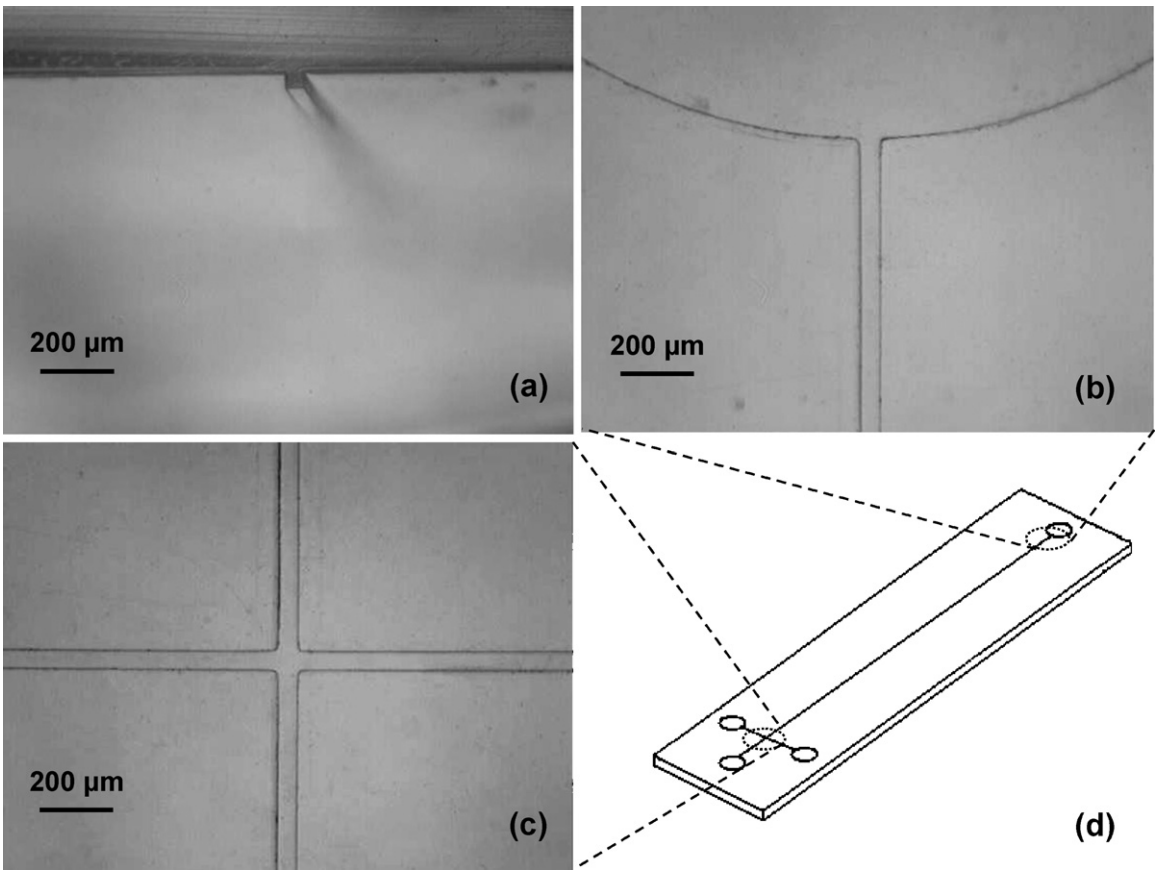

Fig. 3. Microscopic photographs showing (a) the cross section of the channel ridge structure on a gelatin gel template, (b) the injection-cross section, and (c) the interface between the end of a channel and a reservoir port on a PMMA channel plate (d).

microchip. The movable electrode pairs consisted of two 10-μm-thick copper-foil strips (0.8 mm × 10 mm) glued on a piece of PMMA plate (22 mm × 11 mm × 1 mm) using chloroform. The two electrodes were placed in an "anti-parallel" orientation with a distance of 0.8-mm. The detector plate was equipped by two PMMA "clip-like" open-rectangular holders from both shorter ends of the PMMA plate to hold the microchip. In this work, the effective length of the separation channel (from the injection cross to the detection point) was adjusted to be 5.5 cm.

2.6. Electrophoretic procedure

Before use, the channels of the PMMA microchip were rinsed with the running buffer for 10 min. The sample reservoir (Fig. 2l) was filled with a sample solution while the other three reservoirs were all filled with the running buffer. The injections were performed by applying a voltage of +1000 V between the sample reservoir (Fig. 2l) and the grounded outlet reservoir (Fig. 2p) for 2 s while other reservoirs were kept floating. Separations were performed by applying a voltage of +1000 V between the running buffer reservoir (Fig. 2k) and the outlet reservoir (Fig. 2p) and other reservoirs were floating.

3. Results and discussion

A novel fabrication approach was developed in this report for the mass production of PMMA microfluidic chips at low cost using mass-produced gelatin gel templates. The disposable gelatin templates could be easily replicated from SU-8 templates bearing negative relief of channel networks by melting replication and could be mass-produced (Fig. 1A–D). To prepare PMMA microfluidic chips, prepolymerized MMA solution containing a UV-initiator was sandwiched between the disposable gelatin templates and PMMA plates and was allowed to polymerization under UV light to prepare PMMA channel plates at room temperature (Fig. 1E–H). Subsequently, the channel plates and the cover sheets were assembled by plasticizer-assisted thermal bonding (Fig. 2).

Fig. 3a illustrates the microscopic photograph of the cross section of the channel ridge structure on a gelatin gel template. Because gelatin gel is a thermoplastic elastomer with high strength and elasticity, the pattern of the negative relief on the SU-8 template could be easily transferred into the gelatin gel substrate by melting replication with high fidelity. Fig. 3b and 3c shows the microscopic photographs of the injection-cross section and the interface between the end of a channel and a reservoir port on a PMMA channel plate (Fig. 3d), respectively. The results indicated that the raised structure on the gelatin template was successfully replicated into the PMMA substrate after the UV-induced surface polymerization of prepolymerized MMA molding solution. The replication quality of the microstructure on the PMMA channel was satisfactory. Fig. 4a shows the SEM image of the cross section of an unsealed microchannel in the PMMA substrate. In comparison with Fig. 3a, the image of the positive relief on the gelatin template was precisely replicated into the prepared PMMA layer with satisfactory fidelity, indicating a high quality microchannel could be fabricated using the present approach.

In this work, DBP (a plasticizer) was employed in the thermal bonding of PMMA channel plate and covers. The bonding temperature was significantly reduced to 90 °C based on the fact that DBP can decrease the T_g of PMMA [21,22]. Fig. 4b illustrates the SEM

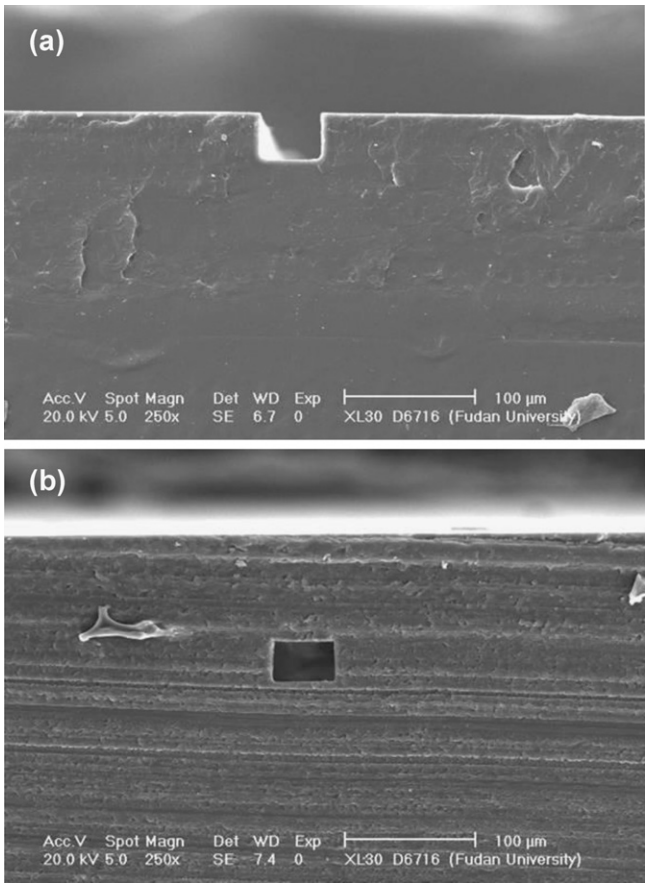

Fig. 4. SEM images of the cross sections of (a) an unsealed microchannel in the PMMA substrate and (b) a channel in a complete PMMA microchip. Accelerating voltage, 20 kV; magnification, 250×.

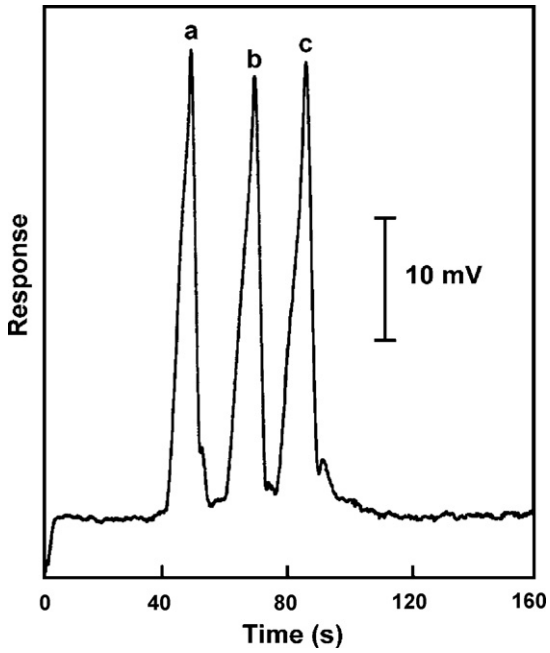

Fig. 5. Electropherogram of a mixture containing (a) potassium, (b) sodium, and (c) lithium (1 mm each). Operation conditions: separation and injection voltage, +1000 V; injection time, 2 s; running buffer, 20 mM boric acid–20 mM tris(hydroxymethyl)aminomethane (pH 8.0); sinus waveform with a frequency of 400 kHz and a peak-to-peak voltage of 5 V; electrode distance, 0.8 mm; electrode width, 0.8 mm.

image of the channel outlet of a PMMA microchip after plasticizer-assisted bonding. The fact that no boundary was observed between the channel plate and the cover sheet indicated that they merged during the bonding process, indicating a high bonding quality. In comparison with the image of the open channel (Fig. 4a) in a PMMA channel plate (Fig. 3d), the deformation of the channel after plasticizer-assisted bonding was minimized because the employed bonding temperature (90 °C) was lower than the T_g of PMMA (105 °C) and the inner surface of the channel did not touch the DBP-coated surfaces of the PMMA cover. In addition, it was found that the bonding of the PMMA microchips with the assistance of DBP was fairly strong, allowing the microchips to be sawed, scraped, polished, filed, broken, and sonicated without debonding.

Because PMMA chips were transparent, optical microscope was used to check their quality. The results indicated that high quality microchips were fabricated using the present method with no observable interspaces along with the absence of air bubbles and voids entrapped. The main channel body and cross section were complete and intact after bonding. The structure transferred into the PMMA material was characterized by a satisfactory precision of the master replication. The reproducibility of such replica molding was studied among 20 PMMA microchips fabricated using gelatin gel templates that were all replicated from the same SU-8 template bearing negative relief of the channel network. Chip-to-chip reproducibility has been found with relative standard deviations (RSDs) of 3.9 and 4.7% for the width (48.8 μm) and the depth (33.2 μm) of the fabricated channels in the final PMMA microchips, respectively.

The gelatin gel templates used in this work contained 42.9% (w/w) water and 21.4% (w/w) glycerol, offering the high hydrophilicity and elasticity of the prepared gelatin templates so that they could be easily separated from the SU-8 negative template and the hydrophobic PMMA channel plates. Gelatin gel templates contained higher content of gelatin owned higher strength. In this work, the content of gelatin in the soft gelatin templates was 35.7% (w/w) considering the viscosity and workability of the molten gel as well as the strength of the templates. The glycerol and water in the gelatin templates served as plasticizers. They were also important solvents that decreased the viscosity of the molten gelatin gel. The electroosmotic flow properties of the prepared PMMA microchips were evaluated using the well-established baseline monitoring technique developed by Huang et al. [23]. The electroosmotic flow value at pH 8.0 was measured to be 2.27×10^{-4} cm^2 V^{-1} s^{-1} at a field strength of 200 V cm^{-1} and was well in agreement with literature values for pure PMMA microchips (1.2×10^{-4} to 2.6×10^{-4} cm^2 V^{-1} s^{-1}) [7].

The analytical performance of the prepared PMMA microchip was demonstrated by the electrophoretic separation of three cations. Fig. 5 illustrates the typical electropherogram of a mixture containing potassium, sodium, and lithium (1 mM each). The PMMA microchip provides baseline-resolved peak shape and high plate numbers (10 362, 18 506 and 26 622 plates/m for potassium, sodium and lithium, respectively). The half peak widths of potassium, sodium, and lithium are 4.8, 5.1, and 5.3 s, respectively, with the corresponding sensitivities of 37.4, 34.1, and 35.0 mV/mM. The precision was evaluated based on 7 repetitive measurements of a sample mixture containing potassium, sodium, and lithium (1 mM each). Reproducible signals were obtained with RSDs of 2.7% (potassium), 3.3% (sodium), and 4.1% (lithium) for the peak heights.

In comparison with PDMS template that we employed to fabricate PMMA microchips [15], the advantages of the present gelatin gel template include low cost, ease of fabrication, low swelling,

and short fabrication time. In addition, it is more environmentally friendly because the naturally degradable template can be reused by melting. To prepare PDMS template, the mixture of PDMS oligomer and cross-linking agent were poured onto a SU-8 master and cured at 70 °C for 60 min. To minimize solvent swelling, it needed to be pretreated at a higher temperature for 6 h [15]. The total fabrication time of PDMS template is 7 h and is much longer than that of gelatin template (10 min). In addition, the present gelatin-based template was composed of 35.7% (w/w), 42.9% (w/w) water, and 21.4% (w/w) glycerol. During the in situ polymerization of the molding solution, its swelling was minimized because it was hydrophilic. More importantly, all materials for the fabrication of gelatin-based template are much cheaper than those used in the preparation of PDMS template, indicating great promise for the low-cost fabrication of PMMA microchips.

4. Conclusions

In conclusion, disposable gelatin gel templates have been successfully employed in this work for the low-cost fabrication of PMMA microfluidic chips in combination with plasticizer-assisted bonding and UV-initiated in situ polymerization. Thermally reversible gelatin gel was an ideal impression material for the mass production of disposable templates because of its low cost, low melting point as well as high strength and elasticity. Because the positive gelatin gel templates were directly replicated from negative SU-8 negative templates by melting replication and could be mass-produced, the fabrication process was significantly simplified. No wet-etching was needed. More importantly, they could be easily separated from both the SU-8 negative template and the molded hydrophobic PMMA channel plates. Another advantage of the gel templates was that they could be easily recycled by melting. The ease, simplicity, versatility, and low cost of the new fabrication route thus make it extremely attractive for the mass production of PMMA microchips. The present fabrication strategy will also find applications in the fabrication of microfluidic chips made from other polymers.

Acknowledgments

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