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Sticker Microfluidics: A Method for Fabrication of Customized Monolithic Microfluidics

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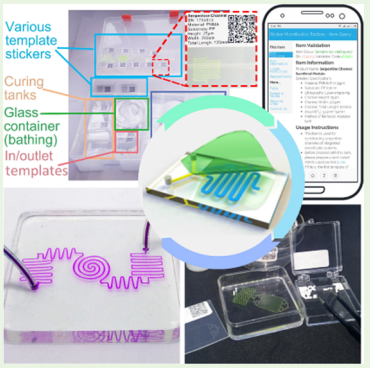
Supporting Information

ABSTRACT: This paper proposes a novel strategy and an all-in-one toolbox that allows instrument-free customization of integrated microfluidic systems. Unlike the modular design of combining multiple microfluidic chips in the previous literature, this work, for the first time, proposes a "template sticker" method, in which sacrificial templates for microfluidic components are batch-produced in the form of standardized stickers and packaged into a toolbox. To create a customized monolithic microfluidic system, the end users only need to select and combine various template stickers following formulated steps. The fabricated microfluidic devices have well-defined microscale features, while the fabrication process is inexpensive and time-saving. Various functional microfluidic devices were fabricated and tested using this toolbox. The capability to create microchannels on curved surfaces is also demonstrated. As a proof of concept, we developed with the proposed toolbox a colorimetric testing platform for the detection of nitrite ions. The sticker toolbox, as the first self-contained portable platform for microfluidic fabrication, allows prompt customization of monolithic devices, enabling deployment of microfluidics with both ideal performance and customizability.



KEYWORDS: *modular microfluidics, sticker toolbox, on-site customization, PDMS*

1. INTRODUCTION

Since its advent in the 1990s,[1] microfluidics has undergone rapid development and become a powerful tool in many fields, such as clinical diagnosis,[2] drug discovery,[3,4] translational medicine,[5] chemistry, biology, and materials science.[6−12] As the fabrication process of microfluidic chips derives from microelectromechanical system (MEMS) techniques, in the early days, the fabrication of a microfluidic chip could be rather complicated and expensive.[13] It was not until the soft-lithography technique emerged[14] and silicone elastomers were used that microfluidics became widely promoted in laboratories. Nevertheless, the soft-lithography technique could only handle relatively uncomplicated structures in one layer, and the fabrication of multilayered structures requires bonding of multiple independent layers, leading to a large number of duplicated iterations. Therefore, this method could be laborious and time-consuming. Other fabrication techniques, such as hot embossing and injection molding,[13,15] also lead to monolayered and stereotyped devices. In these approaches, the inflexible design and the incapability of creating complex three-dimensional (3D) structures set barriers in their on-site deployment.

To address the set-up cost issue and simplify the customization of microfluidic chips, one of the solutions is to switch to novel fabrication techniques. With the help of emerging micromanufacturing techniques, researchers began to switch to novel fabrication approaches to create more complicated microfluidics and lower the setup cost. Among these, 3D printing, known for its automated process and low cost, is especially promising and is employed to fabricate monolithic microfluidic devices.[6,16−20] Microfluidic devices with arbitrary structures are directly printed using 3D printing.[21−23] Molds for microfluidics are also created to enable a mask-free process of casting elastomers.[24] The 3D-printing technique enabled the fabrication of arbitrary 3D structures of microfluidics and is suitable for applications requiring complicated microfluidic structures. Other manufacturing techniques, such as inkjet printing,[25,26] cutting plotting,[27] and micro-milling,[28] also showed great potential in rapidly prototyping microfluidic devices. However, although they are fast and highly customizable, most such approaches suffer from a poor surface quality and coarse features, and at the present stage, they must still depend upon professional instruments and expert operators, setting a hardware limit to on-site customizable applications.

As another effective approach for low-cost and easy-to-use customized microfluidics, modular microfluidics is attracting more and more attention. In modular microfluidics, independent microfluidic blocks are created in reconfigurable design and assembled to form a microfluidic system. In previously reported works,[29−39] microfluidic chips are created in the form of combinable blocks, such as Lego-like blocks,[37−39] Jigsaw-puzzle-

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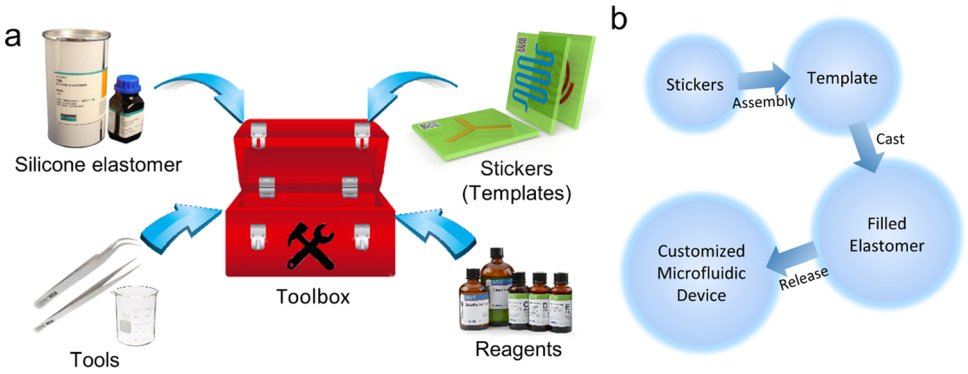

Figure 1. (a) Constitution of a toolbox presented in this paper. (b) Schematic diagram of creating microfluidics with the proposed toolbox.

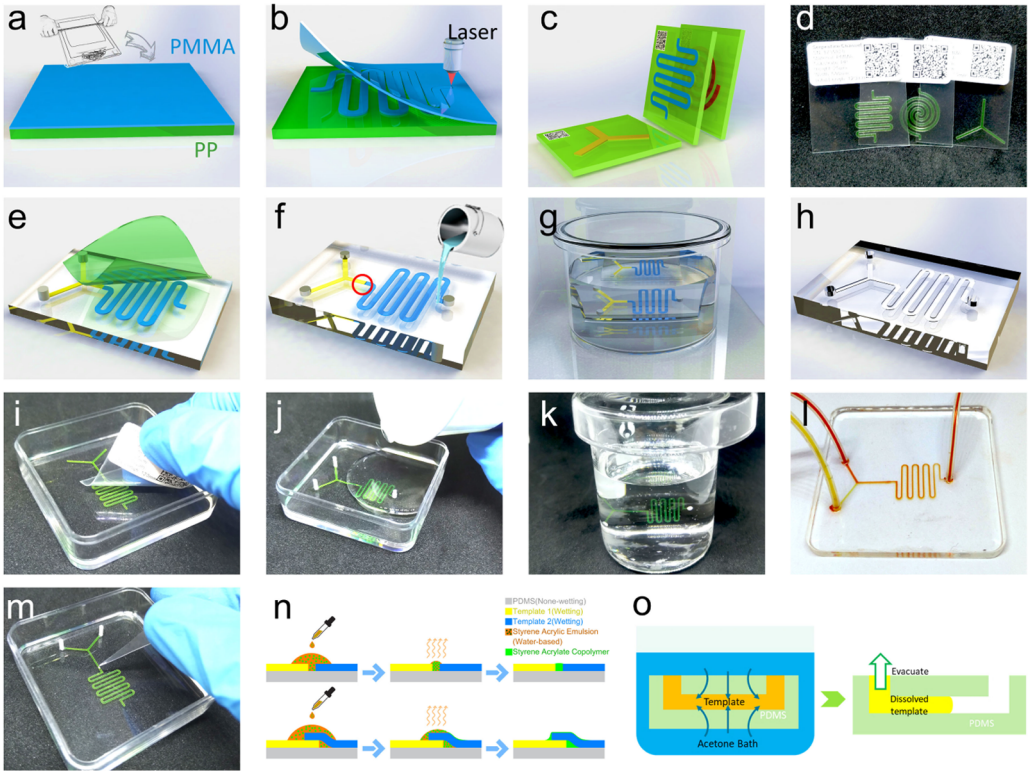

Figure 2. Fabrication process of creating microfluidic devices. (a–c) Schematic illustrations of preparing PMMA stickers on PP backing using laser cutting. (a) Coating the PMMA film on the PP sheet. (b) Laser cutting of PMMA patterns and removal of the unnecessary PMMA film. (c) Stickers of different microfluidic structures. (d) Laser-cut microfluidic stickers. (e–h) Schematic illustrations of creating microfluidics using the stickers. (e) Arranging and sticking the stickers on PDMS substrate. (f) Casting liquid PDMS and curing. (g) Acetone bathing. (h) Completed microfluidic chip. (i–l) Photograph of the process shown in (e)–(g). (m) Photograph of linking separate stickers with styrene acrylate copolymer emulsion. (n) Schematic illustration of wettability-guided emulsion linking of the stickers shown in (f) when two stickers are not in contact (top) and stickers overlap (bottom). (o) Schematic illustration of dissolving the template and evacuating the chip. Left: dissolving the template sticker in an acetone bath. Right: evacuation of the chip.

like blocks,[31] magnetic blocks,[35] and other forms,[32,36] to allow easy and arbitrary docking of microfluidic components. The modular microfluidics enabled rapid on-demand reconstruction and modification of microfluidic systems and provided an economical and easy-to-use solution to customized microfluidics. However, compared with monolithic microfluidic systems, the modular microfluidics has an unstable interconnection between the blocks, resulting in intolerance to harsh conditions, such as high pressure and external forces. Moreover, the liquid residual/loss in the tubing and gaps of connections may lead to inaccurate results. The large space consumption and the prolonged fluid path that are caused by the stacking of multiple microfluidic blocks may also lead to undesired outcomes. As a result, in applications requiring high performance and reliability, such reconfigurable modular systems are not applicable. It would be desirable to determine an approach to construct complex microfluidic systems with both the excellent performance of monolithic microfluidic systems and the good flexibility and convenience of the modular microfluidics.

In this work, we implement a novel strategy of creating customized monolithic microfluidic chips by utilizing a toolbox containing combinable sacrificial templates. Rather than modulating independent microfluidic chips, the templates for various microfluidic functions are created in the form of stickers

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and are connected by a wettability-guided emulsion to give an integrated template for monolithic microfluidics with a complex structure. By simply arranging the stickers and casting elastomers, monolithic microfluidic devices could be obtained directly. In addition to convenience, the toolbox itself is a self-contained platform for microfluidic fabrication, and all of the materials required in the process are factory-packaged and included in the toolbox (Figure 1a), thus, can minimize the requirement for professional knowledge and eliminate the use of external materials and instruments. Equipped with this toolbox, nonexpert end users can easily create monolithic microfluidic devices with only a few formulated steps (Figure 1b). Owing to its on-site reconfiguration capability, the toolbox allows fast prototyping and easy modification of microfluidic structures at low cost, giving an easy and flexible solution for highly customized applications. In addition, the proposed method allows easy fabrication of microchannels on curved surfaces, which could be difficult in traditional approaches. As a proof of concept, microfluidic devices of various functions like mixing and droplet generation were fabricated with this sticker-based technique; an application of continuous monitoring of nitrite ions is also demonstrated using the device fabricated with the toolbox. In summary, this work provides a novel strategy of rapidly creating highly customized microfluidics with minimum requirement, which could be appealing for various microfluidic applications.

2. MATERIALS AND METHODS

2.1. Materials. Poly(methyl methacrylate) (PMMA) resin (Mitsubishi Rayon VH001) from Shanghai D&B Laboratory Equipment Co., Ltd. Poly(dimethylsiloxane) (PDMS) prepolymer and curing agent (Dow Corning Sylgard 184), and silicone surfactant (BYK-347, BYK-Chemie GmbH). Polypropylene (PP) sheets (0.25 mm thick), PMMA sheets (0.2−0.5 mm thick), ABS sticks, PS containers, polystyrene-acrylic copolymer emulsion, and PVA sponges are purchased from Taobao online market. Acetone, ethyl acetate, and other reagents are purchased from Rionlon Bohua (Tianjin) Pharmaceutical & Chemical Co., Ltd.

2.2. Preparing Stickers. For stickers with thickness <200 μm, dissolve PMMA resin in ethyl acetate to give a 15 wt % solution. Add 5 wt % of ethyl lactate and 2 wt % of BYK-347 surfactant to the solution. Coat the PMMA solution on a PP sheet using a Mayer coating rod to give a PMMA membrane (Figure 2a). After the PMMA membrane dried, use a laser engraving machine (Universal Laser system VLS 2.30) to cut the PMMA membrane into microfluidic patterns (channels, junctions, etc.). Remove the unnecessary membrane on the edge (Figure 2b). Paste the labels with information and QR code to each sticker (Figure 2c). The PMMA sticker on PP sheet backing is ready for use (Figure 2d).

For stickers with thickness ≥200 μm, directly cut the PMMA sheet of desired thickness into microfluidic patterns using laser cutting. Immerse the sticker in 2% BYK-347 water solution. Dry the sticker at room temperature.

2.3. Creating Microfluidics. Mix the Sylgard 184 prepolymer and the curing agent with a weight ratio of 10:1. Pour the liquid PDMS mixture into a container, leaving approximately 1.5 mm thick liquid PDMS covering the bottom. After a period of curing (either 30 min at 80 °C or 24 h at 25 °C), directly paste the sticker of the desired structure onto the semicured PDMS surface, then remove the backing of the stickers. The PMMA pattern should be transferred onto the PDMS surface (Figure 2e,i). For creating multiple structures in one device, paste the stickers end to end on the PDMS surface. After all of the stickers are transferred to the surface, drip a drop of polystyrene-acrylate copolymer emulsion (30 wt % of copolymer) at the interconnections of stickers using a plastic stick (Figure 2m). Wet the ABS pillars on one end with the PS-acrylate emulsion, then put ABS pillars at the site of inlets/outlets with the wet end contacting the stickers. Let the emulsion dry at room temperature for 15 min. Cast liquid PDMS onto the stickers (Figure 2f,j). Cure the PDMS (e.g., 80 °C for 2 h). The covering layer of PDMS will cross-link with the bottom PDMS, giving a one-piece PDMS microfluidic chip with templates inside.

2.4. Template Removal. Place the PDMS chip in an acetone bath (Figure 2g,k). After 8−12 h of bathing, take the chip out. The inlet/outlet ABS pillars are dissolved and the inlets/outlets are revealed. Alternately, inject air and acetone into the inlets/outlets to evacuate and rinse the chip. Afterward, dry the chip to let it deswell. The chip is then ready for use (Figure 2h,l).

2.5. Chip Cleaning and Sterilization. For cell-based assays, the devices should undergo an additional cleaning and sterilization process. To do this, infuse 100% ethanol into the device for 5 min to remove contaminants, then the devices were sterilized by applying 70% ethanol for 15 min. For long-term culture, wet autoclave the device for 121 °C for 8 min.

2.6. Sticker and Device Characterization. The scanning electron microscopy (SEM) image of the stickers and channel slices are acquired from FEI Nova Nano SEM 430. The Raman spectra of the PMMA sticker, acetone, pristine PDMS, and released channel surface are acquired using an inVia confocal Raman microscope. For PDMS swell-recovery tests, PDMS blocks are casted and cured in a cuboid container ($l \times w \times h$ = 25 mm × 4 mm × 3 mm) and immersed in acetone overnight. After taking out from the acetone bath, the length of the PDMS block is measured over time.

3. RESULTS AND DISCUSSION

3.1. Designing Sticker Templates. The sticker templates are soluble sacrificial polymer patterns that define the microfluidics. There are several criteria for the selection of this template material: (1) it should have good solubility in one or several solvents for easy removal; (2) it should have good tensile strength to withstand the stress when transferring the template to the silicone elastomer surface; (3) it should be compatible with high-precision patterning techniques; and (4) it should have a moderate molecular weight (M_w), as low M_w polymers are too fragile and may easily crack in the transfer process, and high M_w polymers are usually less soluble and take more time to dissolve. Moreover, price and availability should also be taken into consideration. Several common commercially available polymer materials along with their solvents satisfying these requirements are considered in this study (see Table S1). We finally chose PMMA as the sticker material.

An important accessory of the sticker is the backing, which helps the sticker to retain its shape before pasting. Although thick stickers (thickness ≥ 200 μm) are rigid enough and free from deforming, stickers as thin as 50 μm are too soft to be directly handled in the pasting process. For easy transfer of the sticker, the backing should have an easy-to-release property, indicating a material of low surface energy. However, materials with excessively low surface energy such as poly(tetrafluoroethylene) have problems even before transferring the sticker, because the stickers have too weak adhesion to the backing and easily peel off when handling. The polypropylene (PP) sheet is tested to be an appropriate choice for backing and is used in this study.

To pattern a template sticker, we used a laser cutting method, as illustrated in Figure 2a−c. The details of the patterning process are described in the Section 2. The laser-cut stickers are of good precision and efficiency and are suitable for laboratory uses. However, this does not mean that the end users should have a laser engraving machine in their own lab or in the toolbox. The laser engraving machine is not intended to be a component or accessory of the proposed toolbox. Various kinds of

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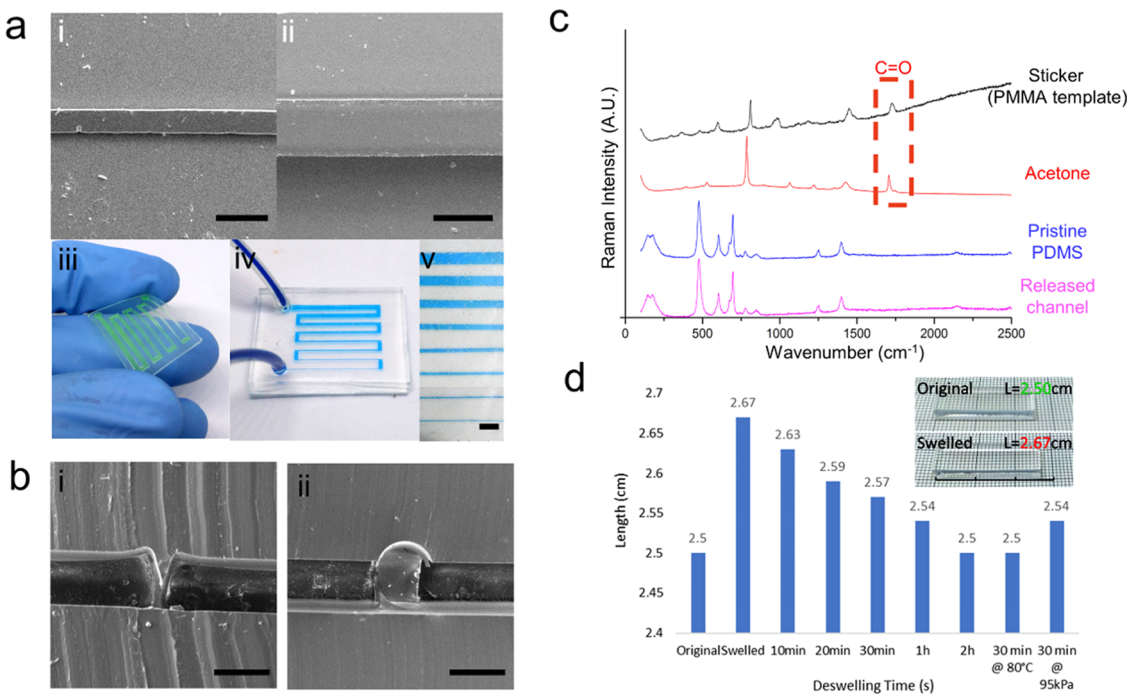

Figure 3. Characterization of the laser-cut stickers and devices. (ai,ii) SEM image of laser-cut stickers transferred on the PDMS substrate with linewidth × thickness of (i) 20 μm × 50 μm and (ii) 200 μm × 500 μm, scale bars represent 100 and 500 μm, respectively. (iii) Photograph of a 20 μm-thick PMMA sticker on a PP backing, the sticker is dyed green. (iv) Linewidth testing device fabricated using the sticker. The microchannels in PDMS is filled with a blue dye solution. (v) Enlarged image of the microchannels. Scale bar represents 1 mm. (b) SEM image of the cross-sectional view of the fabricated microfluidic device at the place of sticker connections. (i) Stickers not connected by emulsion. (ii) Stickers connected with the emulsion. Scale bars represent 200 μm. (c) Raman spectra of the template sticker, solvent (acetone), pristine PDMS, and released channel. (d) Photograph of the PDMS length change over time after taking out of the acetone bath.

prepatterned stickers are included in the box, and it is the combination of stickers rather than the patterning method that allows on-site customization. When it comes to widespread use, the fabrication of stickers would be completed in a sticker factory. The factory will build sticker toolboxes for various purposes according to the professional knowledge, for instance, to include different spiral channels in a cell-sorting toolbox or include tissue-trapping structures and gradient generation stickers in a drug screening toolbox. After purchasing these toolboxes, the end users, who may not be a professional technician on microfluidics, could customize microdevices by just arranging the prefabricated stickers. To prove the batch production capability of the stickers, we also created stickers with a die-cutting method, a method that has already been widely used in industry for processing ordinary stickers. A microcapillary molding technique[40] is also adapted for the fabrication of stickers with precise features. The comparison of these methods and stickers are shown in Figure S1 and Table S2. Besides the above-mentioned methods, other techniques such as screen printing and masked etching could also be employed to create stickers, providing either high efficiency or high precision. Here, for the ease of demonstrating differently structured devices, all of the stickers used in the later processes are created with the laser cutting method.

3.2. Sticker Arrangement and Emulsion Linking. The template stickers are to be pasted end to end to form a complete template for microfluidics. However, the stickers are not as sticky as an ordinary sticker. Instead, the target surface of the stickers should be adhesive to immobilize the stickers. As the most commonly used material for microfluidics, the poly-(dimethylsiloxane) (PDMS) substrate in a semicured state is used as the target substrate for pasting and combining the stickers, as it is adequately adhesive to the stickers and can cross-link with a top layer of PDMS to directly form an enclosed device without an extra bonding process. The process of creating microfluidics using the sticker is shown in Figure 2e–h. The stickers are aligned manually, and the alignment could be checked through an electronic magnifier before being thoroughly stuck to the PDMS substrate. The amendment should be made if a misalignment is found. For connection of very small channels of the stickers, it could take several trials to get a good alignment, and better success rate could be achieved by pasting stickers with connecting ends perpendicular to each other so that there is a higher chance for the two stickers to come into contact. After the stickers are directly pasted to the surface of the PDMS substrate, the release backings are removed. For a device containing multiple templates, all templates are arranged end to end. Ideally, the stickers could have thorough contact with each other. However, when it comes to manual operation, there is always a small gap or a part of overlap between the stickers. Therefore, the templates should be connected to each other before casting a top layer of PDMS to ensure an unblocked structure. To do this, we herein propose a wettability-guided emulsion linking method: a water-based polymer emulsion is dripped at the connections of templates, as illustrated in Figure 2n. The template stickers, as are modified with surfactants, have better wettability than the PDMS substrate, therefore the emulsion will automatedly fill the space between the templates due to the capillary force rather than spreading on the substrate. After a few minutes of drying and polymerization, the templates are thoroughly connected. The ABS inlet/outlet template pillars are placed and connected to the templates in the same manner.

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3.3. Encapsulation and Template Removal. After all sacrificial templates are thoroughly connected, the PDMS prepolymer/curing agent mixture is casted onto the interconnected templates in the curing tank. Liquid PDMS should not immerse the top of inlet/outlet template pillars. An optional degassing process could be employed to eliminate the bubbles, which may exist in the final device. Afterward, the device is cured at either high temperature (80 °C for 2 h) or room temperature (48 h) to achieve an enclosed device with sacrificial templates inside. It is noteworthy that although it is recommended to employ degassing and heated curing to speed up the whole process, they are not compulsory and can be skipped in the absence of the necessary conditions. Therefore, the whole process of fabrication can be totally instrument-free.

The removal of sacrificial templates inside the PDMS chip is different from the ordinary MEMS procedure. In silicon processes, the sacrificial material is dissolved and washed by directly contacting the solvent. As a result, the sacrificial material should be directly exposed to the solvent, and sometimes the removal could be inadequate on sharp edges or requiring additionally etched through holes.[41] In this work, however, the dissolving of sacrificial material does not necessarily require the sacrificial template to be directly exposed to the solvent; owing to the porous nature of PDMS, solvents from outside can permeate the PDMS and dissolve the whole template rather than gradually dissolving from an inlet/outlet. The nanopores in the PDMS matrix work like numerous through holes for solvent transportation, with significantly improved efficiency and comprehensiveness in dissolving sacrificial material compared with ordinary MEMS processes.

Apart from template material solubility, the solvent compatibility with PDMS,[42] especially swelling properties, is another essential consideration in choosing solvents for this process. A solvent with a higher swelling ratio will dissolve the template faster as the swelled PDMS becomes looser, which in turn accelerates diffusion. However, a solvent with an excessively large swelling ratio, such as chloroform, makes the PDMS device too fragile to handle in the evacuation process. Table S1 shows the combinations of template materials and their solvents tested in this work. We finally chose acetone for dissolving PMMA templates and ABS inlet/outlet pillars. Figure 2o illustrates the process of dissolving the template and evacuation of the PDMS chip. The chip is placed in an acetone bath for 8−12 h to completely dissolve the PMMA and ABS, evacuated with a syringe, and then rinsed with acetone to remove the residue. After drying for deswelling (either heated or at room temperature), the fabricated chip will recover to its undeformed state[42] and become ready for use.

Comparing the fabrication process of the sticker method with standard soft lithography, the sticker method could be much simpler. In this method, the users will only need to paste the stickers, cast PDMS, and release the channels in the solvent, every step could be learnt by nontechnicians. On the other hand, the standard soft lithography includes a complex process flow of spin coating, baking, exposing, developing, punching inlets/outlets, plasma bonding, etc. Many of the processes depend on professional instruments and need a strict condition control, and a skilled technician may fail due to a single mistake in any of the steps.

3.4. Characterization of the Stickers and Devices. SEM images of the laser-cut stickers are shown in Figure 3a. We successfully created stickers on a PMMA film with a lateral convex feature size of 50 μm using laser cutting. This linewidth is dependent on the resolution of the laser cutting machine and still has room for improvement. Figure 3ai is the SEM image of a 50 μm-wide laser-cut sticker with a thickness of 20 μm, and Figure 3aii is a sticker that is 500 μm wide and 200 μm thick. The results show that laser cutting is capable of handling a wide range of thickness and linewidth of the stickers. In our practice, the thickness of the sticker could be as small as 5 μm using Mayer rod-coated PMMA films, and even smaller thickness is possible through spin-coating. However, because of the brittleness of the sticker and resulting problems in patterning and transferring, excessively thin stickers may become unpractical in application. Typically, the process of creating a PMMA sticker of moderate complexity (e.g., a serpentine channel with a total length of 100 mm) can be done within 1 min using laser cutting, and the overall cost per sticker is estimated as less than $0.01. However, there are also drawbacks of the laser cutting method, such as high setup cost, heat-induced deformation and flaws (Figure S2). It is noteworthy that the stickers here are created using laser cutting only for convenience of demonstration, and when it comes to scale application, mature techniques in the industry such as die-cutting and masked etching could be used to create stickers with high efficiency and precision at minimum cost. The stickers and the final fluid channels created with the stickers share identical profiles but have complementary geometries; thus, we are able to create microchannels with a minimum concave lateral feature size of 50 μm and a channel depth down to 5 μm using laser cutting. Figure 3aiii−v shows the photograph of a PMMA sticker on a PP substrate and optical images of the microfluidic device fabricated with the sticker. This sticker has a thickness of 20 μm and a changing linewidth from 1000 to 50 μm, so is the resulting devices.

To demonstrate the necessity of linking the templates in the multisticker process, we fabricated interconnected microchannels with assembled stickers. Figure 3b shows the SEM images of the slices of devices from stickers without and with the emulsion linking. The unlinked stickers, although in contact with each other by naked eyes, still have, actually, a small gap between them, therefore, the resulting channel is partially blocked by PDMS. Meanwhile, for the stickers apparently not in contact with each other, the emulsion linking gives microfluidic channels a thorough connection, ensuring an unblocked fluid path.

To determine the immersion time required for template removal in the acetone bath, we used finite-element analysis to study the diffusion behavior of acetone through PDMS. According to the previous literature, acetone can diffuse particularly fast in PDMS with an effective diffusion coefficient of about 3×10^{-10} m^2/s.[43,44] We simulated the acetone penetration process from the PDMS surface to the inside sticker templates (Figure S3). The results show that it takes about 4 h for acetone to reach a thorough diffusion in 4 mm-thick PDMS, at which time the template inside the PDMS could be regarded as directly contacting acetone, giving a fast-dissolving speed of the sacrificial templates. Further experiments showed that the time required for a thorough dissolution of the stickers ranges from 8 to 12 h, with dependence on the chip and template thickness.

After the chip is evacuated and dried, we are interested in how much of the PMMA template and acetone remain on the surface of microfluidic channels after release, as residual may influence on-chip reactions. Figure 3c is the Raman spectra of the stickers, acetone, the pristine PDMS surface, and the surface of released channels. It can be observed that the released channels showed

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no significant difference from pristine PDMS, and the characteristic peak of the PMMA sticker and acetone (C═O double bond) is not observed, which means no significant residuals are left on the surface of the channel, indicating that the fabricated devices could be suitable for cell-related applications after proper cleaning and sterilization processes. Figure 3d shows the swell-recovery test of the microfluidic chip. Bulk microfluidic blocks with length L = 2.5 cm were casted in the same mold and immersed in acetone overnight. At t = 0, the PDMS blocks were taken out of the acetone bath and the length change of the PDMS blocks was measured over time. It can be observed that at room temperature and pressure it takes 2 h to recover to an undeformed state. Moreover, heating and vacuum degassing will accelerate the recovery process.

3.5. Creating Microfluidics on Curved Surface. Microfluidic channels on curved surfaces could be very useful for various applications. For instance, in wearable[45] and implantable devices,[46] there is a need to create microfluidic channels on curved surfaces to give conformal geometry of fluid channels. However, creating microfluidic channels on curved surfaces could be challenging through traditional measures. In this work, we also demonstrated creating microfluidic channels on curved surfaces. Figure 4 shows the Illustration and photographs of this approach. By simply sticking stickers on the curved PDMS substrate and apply the cast-release process, microfluidic devices with curved channels could be built. Such devices could be useful in creating curved voids like blood vessel constructs of organs.

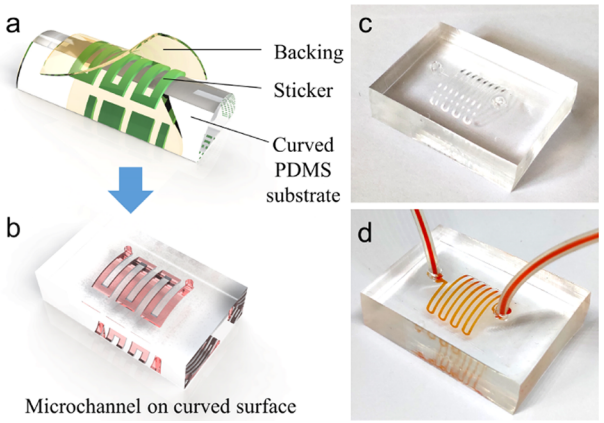

Figure 4. Microfluidics on curved surfaces. (a) Illustration of pasting the sticker on a curved substrate. (b) Illustration of a microfluidic device created using the curved sticker. (c, d) Photograph of a microfluidic device with channels on the curved surface.

3.6. Limitations of the Sticker Method. Apart from the aforementioned advantages, there are also limitations of the sticker method. One major limitation could be the overall time consumption from concept to device. The typical time to fabricate a microfluidic chip could be 10 h or more, depending on the sticker and chip thickness. This duration is acceptable for applications that permit an overnight delay but could be too long for emergency use. Supplementary means, like heating and ultrasonication, could be used to accelerate the release and deswelling process and speed up fabrication, but consequently require more equipment. Another limitation could be the inadequate removal of the template inside. The removal of template stickers is checked by the naked eye, so there could be residuals of templates in the released channels that are difficult to notice. Following the recommended dissolving time and additional ultrasonication could help remove the template thoroughly. A third limitation is the imperfections due to manual operation. There should be imperfect features (typically a larger local channel width) at the places of sticker connections due to the manual alignment and linking of the stickers. Still, the stickers could give properly working devices when the design is not sensitive to these local imperfections. The use of self-healing materials as the sticker template may help resolve this issue through an automated and reagent-free linking process.

3.7. Toolbox for Microfluidics Customization. To enable the fabrication of customized microfluidic devices in the arbitrary environment, we proposed a toolbox with all of the conditions required for the process of fabrication, as shown in Figure 5a. Apart from various types of stickers, other necessary materials like inlet/outlet pillars, silicone elastomer, curing agent, solvents of the sticker, tools, and containers. Each item in the toolbox has a label containing the description of the item and a QR code, scanning the QR code leads to a webpage of detailed information and usage instructions for the item (see Figure 5b). By following the instructions on the webpage (Figure 5c), nonexpert users will be able to create customized microfluidics with the contents of the toolbox (Figure 5d). At the present stage, we have included the toolbox with the stickers of commonly used microfluidic structures, including various types of channels and junctions, and functional components such as mixers, gradient generators, reaction chambers, etc., as shown in

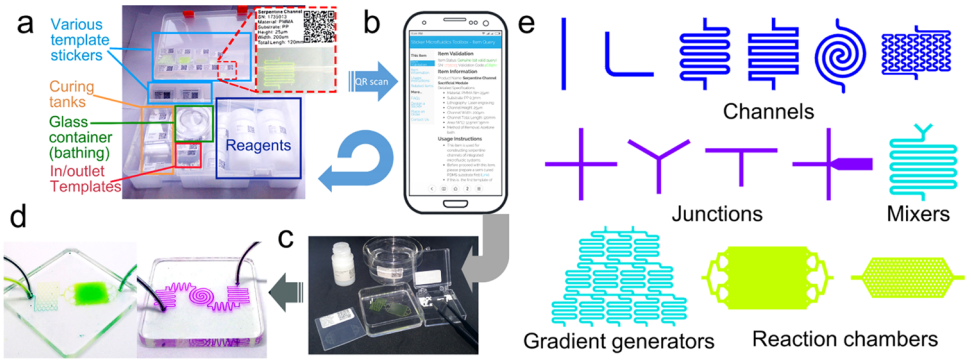

Figure 5. Sticker toolbox for microfluidics customization. (a) Constitution of the toolbox. Inset: the enlarged image of a serpentine channel sticker. (b) Web page on mobile devices displaying the detailed information and usage instructions of the sticker. (c) Creating the microfluidic device using the toolbox. (d) Devices fabricated using the toolbox. (e) Some basic patterns of stickers included in the toolbox.

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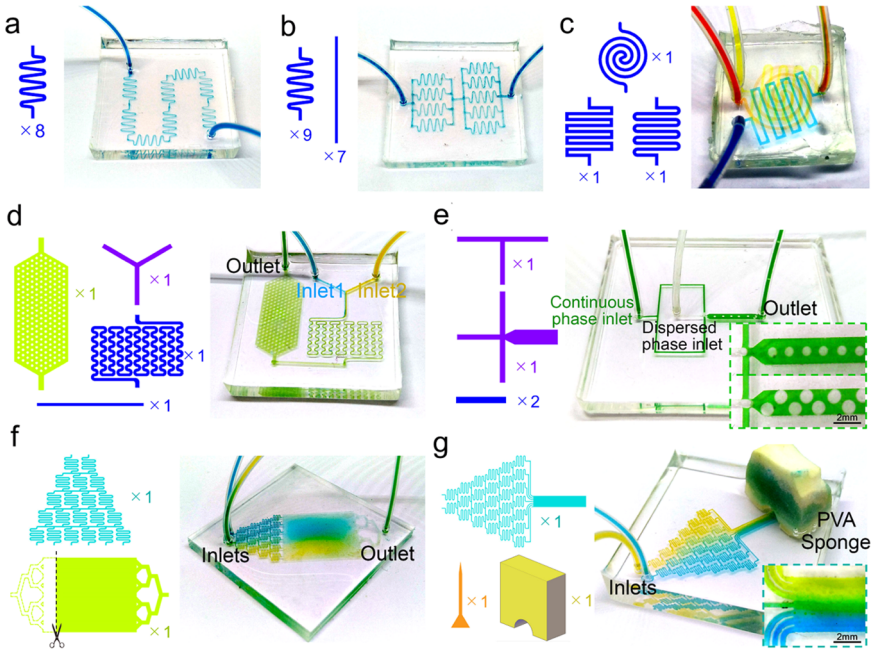

Figure 6. Microfluidics fabricated with the sticker toolbox. (a) Serial-connected zigzag channels created with eight zigzag channel stickers. (b) Parallel-connected zigzag channels created with 9 zigzag channel stickers and 7 straight channel stickers. (c) Device of 3 layers of channels created with 1 spiral channel sticker, 1 right-angle stacking channel sticker, and 1 serpentine channel sticker. (d) Mixing reaction chamber created with a Y-junction sticker, a stacked serpentine channel sticker, a straight channel sticker, and a reaction chamber sticker. (e) Droplet generator created with a T-junction sticker, a flow-focusing junction sticker, and straight channel stickers. (f) Chemotaxis chamber created with a gradient generator sticker and a tailored reaction chamber sticker. (g) Passive gradient generator created with a gradient generator sticker, a PMMA needle, and a cubic PVA sponge. The PVA sponge is hydrophilic and could provide a continuous driving force to the aqueous flow.

Table 1. Comparison of the Proposed Method and Other Techniques

		previously reported works			
method	this work	soft lithography	SLA 3D printing	Razor-printing	xurography
X−*Y* resolution	25 μm[a]	20 μm	100 μm	20 μm	20 μm
Z resolution	5 μm	5 μm	100 μm	5 μm	60 μm
minimum lateral feature size	50 μm[a]	20 μm	∼200 μm	100−150 μm	∼200 μm
equipment	toolbox[b]	lithography machine, plasma generator	3D printer	cutting plotter	cutting plotter, plasma generator
chip material	elastomer	elastomer	acrylate resin	polymer tape	elastomer
consumables	sticker	photoresist	acrylate resin	polymer tape	polymer tape
bonding process	no	oxygen plasma	no	no	oxygen plasma
time consumption	10−12 h	48 h	4−8 h	1−4 h	<1 h
estimated cost per device[c]	∼$0.5	∼$200	∼$10	<$0.05	∼$0.66
requirement on expertise	low	high	high	medium	medium
reference		14	19	52	53

[a]*X*−*Y* resolution and minimum feature size refer to laser-engraved stickers. The value could vary with different fabrication methods of stickers. For detailed information, see Table S2. [b]For end users, the toolbox contains the factory-packaged sticker templates, so instruments for sticker patterning like laser engraving machine and cutting plotter are not required. [c]Estimated cost is calculated for material and energy consumption of each customized device. The cost of the system setup is not counted.

Figure 5e. The combination of these patterns allows on-site customization of the arbitrary microfluidic structure.

3.8. Configuring Microfluidics with the Sticker Toolbox. A practical microfluidic system usually consisted of several functional parts for different uses. For instance, a micromixer for sample preparation, a reaction chamber for incubation, a droplet generator for parallel reactions, etc. With the newly proposed toolbox, most of these microfluidic structures could be on-site integrated into a monolithic microfluidic chip. As a proof of concept, we created various types of functional microfluidic devices using the toolbox.

3.8.1. Serial, Parallel, and Multilayered Connections for Microfluidics. Figures 6a and 6b show microfluidic devices with serial- and parallel-connected structures. The fabrication of such devices requires connecting a large number of stickers, and the results show that every channel in the PDMS is thoroughly connected, proving that the emulsion linking method of stickers is robust and repeatable. Figure 6c shows a microfluidic device with three layers of channels. This device is created by repeating the pasting−casting procedure after curing a previous layer. The results proved that the proposed method is capable of handling complex, 3D-stacked microfluidic structures.

3.8.2. Mixing. Mixing is a basic function of microfluidics and is widely used in a large variety of applications.[47] Figure 6d shows of a customized micromixer connected with a reaction chamber. The device is created with a Y-junction sticker, a

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stacked serpentine channel sticker, a straight channel sticker, and a reaction chamber sticker. This device could provide thorough mixing of reagents. After two different dye solutions are injected into the inlets, they are gradually mixed in the stacked serpentine channel and finally homogenously fill the reaction chamber.

3.8.3. Droplet Generation. Droplets are essential in microfluidics as they enabled large throughput of parallel reactions.[48] Figure 6e shows a flow-focusing droplet generator which is created with a T-junction sticker, a flow-focusing junction sticker, and straight channel stickers. The device is capable of generating droplets of different sizes.

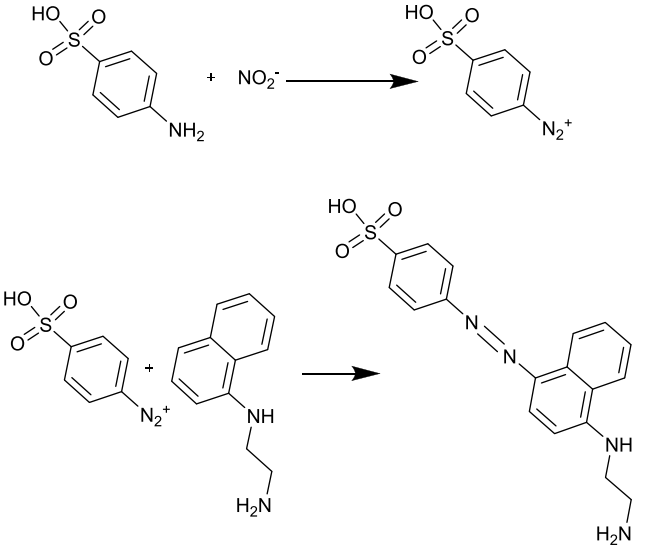
3.8.4. Chemotaxis Chamber. Beside the factory-packaged stickers, end users of the toolbox can even tailor a sticker to fit their own purposes, for instance, a chemotaxis device consisted of a gradient sticker and half of a reaction chamber sticker (cut with scissor), as shown in Figure 6f. The device could generate one-dimensional gradient in a large chamber, which is suitable for chemotaxis studies.[49]

3.8.5. Passive Gradient Generation and Other Components. In applications like the drug screening and chemotaxis study where a gradient concentration of the solution is required, a gradient generator is necessary.[50] Figure 6g shows a gradient generator created with a gradient generator sticker. Apart from the gradient generator sticker, a PVA sponge cube is used as an additional module and connected to the end of the gradient generator before casting the top layer of PDMS. Differing from the previous design where PDMS foam is rendered hydrophilic and grafted with PVA on its surface,[51] in this work, a hydrophilic PVA foam is directly used as an integrated passive capillary pump, providing a continuous driving force to the fluid flow.

3.9. Comparison to Other Methods. Table 1 shows a comparison of the proposed technique and other methods. Using laser-engraved stickers, the microfluidic devices created have a minimum lateral feature size of 50 μm, still less precise than soft-lithography, but fine enough for most microfluidic applications. In comparison with other previously reported techniques like Razor-printing[52] and Xurography,[53] the proposed method requires minimum equipment and expertise: end users could build customized microfluidic devices by arranging ready-made stickers, so the users do not need to handle complicated instruments nor should they use CAD software. The fabrication could take over 10 h and is not faster than the traditional casting−bonding procedure using a ready-made mold. Still, as the proposed method allows on-site designing and fabrication, the whole process of customization does not require starting over from drawing a photoresist mask, so the overall time consumption of this technique could be less than the traditional SU-8 process. In one word, the proposed method could be useful for frontline researchers who have little engineering background to easily and promptly create customized microfluidic devices.

3.10. Application: Continuous Monitoring of Nitrite Ions in Water Using Devices Fabricated with the Toolbox. As a proof of concept, here, we show an exemplary application of continuous monitoring of nitrite ions in water. The monitoring of nitrite ions is important in the food and aquiculture industry. However, the commonly used colorimetric detection could not meet the need for continuous monitoring due to repeated sampling and high consumption of reagents. Here, we designed and fabricated a microfluidic analysis system that could perform continuous colorimetric monitoring of nitrite ions at very low consumption of sample and reagents using microfluidics fabricated with the proposed toolbox.

Figure 7a shows the sticker-based fabrication of the microfluidic device. There are two layers of stickers: on the bottom layer is a Y-junction (red) and a serpentine channel (blue), on the top layer is a straight channel (green). The two layers are connected by an ABS pillar (yellow), which is also the template of the colorimetric chamber. After casting and curing, the channels are released in acetone and become ready for use (Figure 7b). For the detection of nitrite ions, the sample and the colorimetric reagent are infused to the two inlets of the chip. The sample is the sodium nitrite solution with $NaNO_2$ concentration ranging from 0 to 5 mg/L. For the preparation of the colorimetric reagent, sulfanilic acid solution (4 g/L) and *N*-(1-naphthyl) ethylenediamine dihydrochloride solution (2 g/L) are 1:1 mixed and then diluted in deionized water to form a 1:5 dilution. After the two samples and reagent flow meet in the Y-junction, the following reaction occurs:



This reaction is also known as the Griess test. In the presence of nitrite ions, the reaction produces a red-violet diazo dye, and the color depth of the liquid could be used to determine the concentration of nitrite.

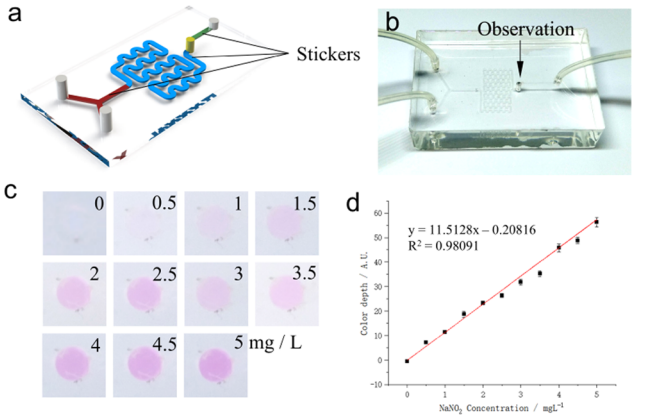


Figure 7. Colorimetric detection of nitrite ions in a sticker-fabricated device. (a) Assembly of the stickers. (b) Fabricated microfluidic device. (c) Photographs captured at the calorimetric chamber with a varying $NaNO_2$ concentration. (d) Color depth versus $NaNO_2$ concentration.

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After a thorough mixing in the serpentine channel, the sample−reagent mixture is then collected in the colorimetric chamber. After 10 min of stable flow, the optic image of the calorimetric chamber is captured by a smartphone camera (Figure 7c). A MATLAB script is written to calculate the color depth from the images. As the color of diazo dye is close to the standard magenta color, the images are first converted to the CMYK color model, and the average value of the magenta channel at the center of images is calculated for the color depth. To avoid the disturbance caused by ambient light, the average value of magenta of the background is deducted from the result. Figure 7d shows the calculated color depth versus $NaNO_2$ concentration. The device showed good linearity for nitrite detection. As the flow of sample and reagent is very slow (2 μL/min) in continuous operation, such device could be useful in long-term monitoring of nitrite ions that require low sample and reagent consumption, like in a fermentation production line or an aquarium.

4. CONCLUSIONS

In summary, we have proposed a novel method for the fabrication of customized one-piece microfluidic systems. With the factory-packaged template stickers, the whole fabrication of microfluidic chips could be completed within a few steps without requiring professional instruments. The fabricated devices have well-defined microscale features and are suitable for most microfluidic applications, such as mixing and droplet generation. We have designed, built, and tested an all-in-one toolbox that utilizes the sticker-template method for the customization of microfluidic systems. As a proof of concept, we fabricated microfluidic devices like micromixers and droplet generators with this sticker-based technique. We also demonstrated the application of continuous monitoring of nitrite ions using the device fabricated with the toolbox. Integrated with various types of template stickers and all necessary materials, the toolbox provides the first self-contained portable platform for the fabrication of highly customized microfluidic systems. In the future, we would like to further explore strategies to create more microfluidic components in a microfluidic system using this method, and templates for other microfluidic components, such as electrodes, active pumps, valves, and different types of sensors, shall also be included in the next version of our toolbox. We also plan to add simulation functions to the user guide web page to help users design the devices and predict the fluid operation, and to create stickers composed of self-healing polymer materials to allow automatic and fail-safe arrangement of stickers. We believe that the accomplishment of our work will benefit the entire community by providing a cost-effective, easy-to-use, and instrument-free method of fabricating customized one-piece microfluidic systems.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsbiomaterials.9b00953.

Comparison of different templates and solvent combination; image and comparison of stickers created using different methods; numerical simulation of acetone penetration through PDMS (PDF)

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This manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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