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Fabrication of Robust Hydrogel Coatings on Polydimethylsiloxane Substrates Using Micropillar Anchor Structures with Chemical Surface Modification

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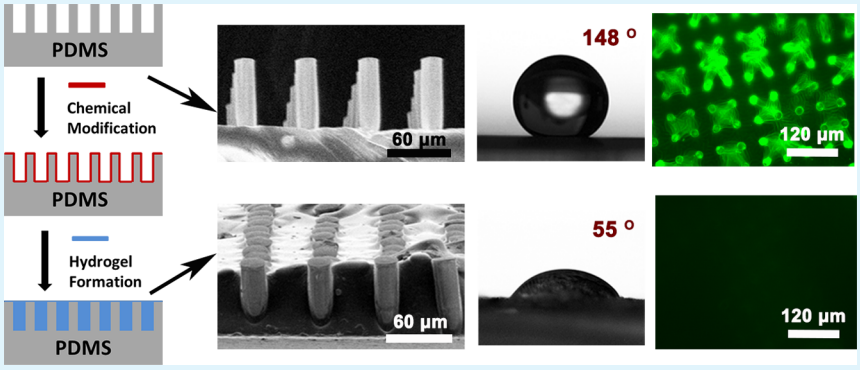
Supporting Information



ABSTRACT: A durable hydrophilic and protein-resistant surface of polydimethylsiloxane (PDMS) based devices is desirable in many biomedical applications such as implantable and microfluidic devices. This paper describes a stable antifouling hydrogel coating on PDMS surfaces. The coating method combines chemical modification and surface microstructure fabrication of PDMS substrates. Three-(trimethoxysilyl)propyl methacrylates containing C═C groups were used to modify PDMS surfaces with micropillar array structures fabricated by a replica molding method. The micropillar structures increase the surface area of PDMS surfaces, which facilitates secure bonding with a hydrogel coating compared to flat PMDS surfaces. The adhesion properties of the hydrogel coating on PDMS substrates were characterized using bending, stretching and water immersion tests. Long-term hydrophilic stability (maintaining a contact angle of 55° for a month) and a low protein adsorption property (35 ng/cm^2 of adsorbed BSA-FITC) of the hydrogel coated PDMS were demonstrated. This coating method is suitable for PDMS modification with most crosslinkable polymers containing C═C groups, which can be useful for improving the anti-biofouling performance of PDMS-based biomedical microdevices.

KEYWORDS: *polydimethylsiloxane (PDMS), micropillar structure, surface modification, hydrogel coating, antifouling*

1. INTRODUCTION

PDMS-based elastomers have been widely used to manufacture biomedical implants such as contact lenses,[1] catheters,[2] and prosthetics.[3] The development of new technologies such as bio-microelectromechanical systems (Bio-MEMS) have further extended the applications of PDMS devices in sensing,[4,5] drug release,[6,7] and diagnostics.[8,9] The advantages of PDMS elastomers include low manufacturing costs, easy fabrication, optical transparency, non-toxicity, gas permeability, mechanical stability, and biocompatibility.[10,11] However, the highly hydrophobic nature of PMDS often makes the surface easily contaminated by biomolecules and may inhibit aqueous fluid flow rates due to surface tension, which extremely limit the application of PDMS in bioanalytical devices and medical/surgical implants.[12,13] For instance, undesirable adsorption of proteins on PDMS surfaces in sensors can interfere with the analysis of biofluids and may cause thrombosis and clotting when in contact with blood.[14,15]

To date, various methods have been proposed to increase the hydrophilicity of PDMS surfaces and reduce nonspecific protein fouling. Oxidization of PDMS surfaces using UV-ozone or plasma, and surface coating/grafting of hydrophilic polymers have been reported.[16,17] Besides, non-covalently bonded polymer coatings on PDMS pillar surfaces were studied by Gupta's group to enhance the hydrophilicity and control the self-assembly of pillars on PDMS substrates.[18,19]

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However, at the molecular level, these often suffer from hydrophobic regeneration owing to the migration of un-cross-linked PDMS oligomers and the rearrangement of PDMS polymer chains at the surface.[13,20] The hydrophilicity of PDMS surfaces modified by some of these methods may only last a few hours or sometimes just a few minutes.[21] Furthermore, the molecular coatings are prone to oxidation, decomposition or being scratched, making the surface hydrophilicity difficult to maintain. Coating PDMS with hydrophilic materials, such as hydrogels, may offer a thicker, more durable and effective coating.[22]

Poly(ethylene glycol) (PEG) is established as a biocompatible and highly protein-resistant coating and is frequently employed in hydrogel fabrication and surface modification of biomedical devices.[23−26] The properties of a PEG hydrogel, such as mechanical strength, water uptake ability, and microstructure, can be easily adjusted by using PEG monomers with different molecular weights.[27,28] As an antifouling polymer, PEG possesses weakly basic ether linkages in molecular structure and low polymer−water interfacial energy (below 5 mJ/m^2), reducing the protein binding potential to PEG surfaces.[29,30] However, hydrogel coatings on PDMS surfaces have rarely been reported, which is probably due to the distinct discrepancy between physiochemical properties of hydrogels (hydrophilic) and PDMS (hydrophobic) materials that makes interfacial connection difficult.

In this paper, we present a facile method of forming PEG hydrogel coatings on PDMS substrates by a combination of chemical modification and the creation of micropillar anchoring structures on PDMS surfaces. The properties of hydrogel coated surfaces were investigated and the antifouling capability was characterized.

2. EXPERIMENTAL SECTION

2.1. Materials. PDMS prepolymer (Sylgard 184 Silicone Elastomer kit) was purchased from Dow Corning Corporation, Canada. 3-(Trimethoxysilyl)propyl methacrylate (TMSPMA), poly(ethylene glycol) diacrylate (PEGDA700, average Mn: 700), 2-hydroxy-1-(4-(hydroxyethoxy)phenyl)-2-methyl-1-propanone (Irgacure 2959), and fluorescein isothiocyanate-labled bovine serum albumin (BSA-FITC) were obtained from Sigma-Aldrich (Ontario, Canada). Fluorescein isothiocyanate-labeled mouse anti-goat IgG (IgG-FITC) was purchased from Santa Cruz Biotechnology, Inc. (SantaCruz, CA, U.S.A.).

2.2. Preparation of PDMS Micropillar Substrates. PDMS substrates with micropillar structures were fabricated by a replica micromolding method. The mold was made of a photosensitive polymer, SU-8 2150 (MicroChem Corp., MA, U.S.A.), using the method previously developed by our group.[31] To fabricate the micropillars substrate, Sylgard 184 silicone prepolymer and curing agents were mixed thoroughly with the weight ratio 10:1. Then, the mixture was poured into the SU-8 mold and degassed under vacuum. After curing at 60 °C for 4 h, the PDMS substrate was peeled off from the mold and cut into proper size for following experiments.

2.3. Surface Chemical Modification and Hydrogel Coating Formation on PDMS Micropillar Substrates. PDMS micropillar substrates were first treated by air plasma (200 mTorr pressure, 30 W power) for 1 min and then immersed in a solution of $H_2O/H_2O_2/HCl$ with a volume ratio of 5:1:1 for 5 min. After rinsing with distilled water, PDMS substrates were immersed in a 1.5% TMSPMA solution of ethanol/H2O (volume ratio, 1:1) for 1 h. The PDMS substrates were then washed with distilled water and dried with N_2.

To prepare a hydrogel precursor solution, 50% (w/w) PEGDA700 macromers were dissolved in 80% (v/v) ethanol and 0.8% (w/w) Irgacure 2959 was added in the solution as a photoinitiator. To fabricate the hydrogel film on PDMS micropillar substrates, the precursor solution was pipetted and filled into the space among micropillars on PDMS by capillary action. After the micropillar substrate was full of hydrogel precursor solution, a thin coverslip plate was placed on the pillars manually. The substrate was exposed under UV light (about 360 nm, 3.0 mW/cm^2) for 3 min to cure the hydrogel. The resulting samples were hydrated in phosphate buffered saline (PBS, pH 7.4) overnight for further characterization.

2.4. Characterization. *Characteristic Chemical Groups Analysis.* Attenuated total reflection fourier transform infrared spectroscopy (ATR-FTIR, Cary 600 Series FTIR Spectrometer, Agilent Technologies, U.S.A.) was used to measure the characteristic chemical groups on the PDMS surface following chemical modification and formation of a hydrogel film. The chemically treated samples were rinsed with distilled water and dried with N_2 and the sample with hydrogel was measured directly after hydrogel formation.

Surface Morphology Analysis. A stereo microscope (Olympus SZ61, Olympus Imaging America Inc., PA, U.S.A.) and a field emission scanning electron microscopy (SEM, Hitachi S-4800, Japan) were employed to observe the morphology of micropillars structure and hydrogel film on PDMS substrates. The samples coated with hydrogel were dried in air before SEM observation.

Adhesion Analysis. The adhesive ability of the hydrogel to the PDMS was investigated qualitatively using a bending test, a tensile test, and by immersion in water. The PDMS substrates were bent with tweezers and stretched parallelly to the hydrogel coatings until failure at the speed of 10 mm/min by using a multi-purpose tensile tester (KES-G1, Kato Tech Co., Ltd. Japan). The samples for stretching were 1.2 mm in thickness and 10 mm in width. During the bending and stretching process, the geometric variation of hydrogel coatings on the substrate was observed. The adhesion strengths of hydrogel coatings on different PDMS substrates were also quantified by de-bonding the two materials. Force-deformation curves were recorded by a thermomechanical analyzer (TMA 2940-Q series, TA Instruments, DE, U.S.A.), and adhesion strength was recorded. The tested samples were round shape with a diameter of 3.5 mm. All the tests (four samples for each test) were performed at 21 °C with an applied force rate of 0.02 N/min.

Contact Angle (CA) Analysis. The images of CAs on different PDMS micropillars substrates, including substrates without chemical treatment, substrates after chemical treatment and substrates coated with hydrogel, were taken by a stereo microscope (Olympus SZ61). The values of CAs were then quantified using image analysis software ImageJ. All the samples were measured at ambient humidity and temperature. For each measurement, a drop of 5 μL distilled water was applied to the sample surface and an image was taken after 30 s. The average CA value for each sample was obtained based on 5 values of CA on different locations.

2.5. Protein Adsorption Test. Fluorecently tagged IgG-FITC and BSA-FITC were chose as model proteins for adsorption test. Prior to protein adsorption, both hydrogel-coated and uncoated PDMS substrates were placed overnight in phosphate buffered saline (PBS) solution (pH 7.4).

Qualitative Analysis. Equal volumes of IgG-FITC solution (0.1 mg/mL in PBS) were spread on the surface of each sample, and then, the samples were kept in a dark and humid environment for 24 h at 37 °C. After being rinsed 5 times with fresh PBS solution, the protein adsorbed on PDMS substrates was detected using a fluorescence microscope (Nikon Eclipse TE 2000-U). The adsorbed protein was presented as the relative fluorescence intensity of the image by processing with ImageJ.

Quantitive Analysis. BSA-FITC solution, 0.1 mg/mL for 2 h and 1 mg/mL for 0.5 h were applied on PDMS samples. Following the incubation, the samples were first washed thoroughly with PBS to remove loosely adsorbed proteins and dried in air. Then, the adsorbed protein was detached with 1% (w/v) sodium dodecyl sulfate (SDS) in a shaker at 37 °C. The fluorescence intensity of the detached proteins was measured using a fluorescence plate reader (Thermo Electron Corporation). The quantity of BSA-FITC adsorbed was calculated using a calibration curve derived from known protein concentration solutions. All experiments were performed five times to get the average values.

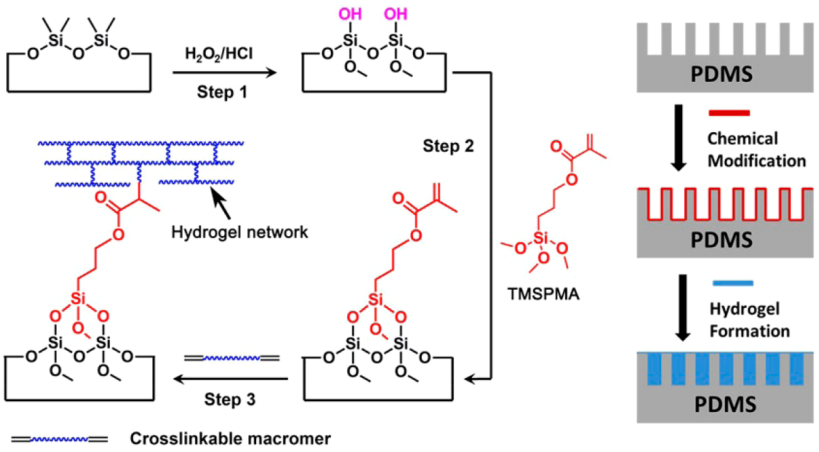

Figure 1. Schematic of PDMS surface modification to form hydrogel coatings.

3. RESULTS AND DISCUSSION

3.1. Preparation of Hydrogel Film on PDMS Substrates. The chemical modification and hydrogel formation on the PDMS substrates are schematically depicted in Figure 1. Firstly, PDMS was oxidized by air plasma and $H_2O/H_2O_2/HCl$ solution to generate superficial hydroxyl groups. Then TMSPMA, which acts as an adhesive to chemically bond the PDMS and the hydrogel coating together, was introduced onto the PDMS surface by silanization. Finally, the hydrogel coating was formed by pouring the hydrogel precursor solution among the micropillars, followed by photopolymerization under UV light. Besides UV-initiated photopolymerization, we also fabricated the hydrogel coatings on PDMS surfaces by thermal polymerization using a redox initiator system (1% w/v ammonium persulfate/tetramethylethylenediamine, 3 min at 40−50 °C). The hydrogel coatings formed by thermal polymerization has little difference in properties compared with the ones formed by UV polymerization, which provides an alternative method to fabricate hydrogel coatings when UV is not available.

The variation of surface chemical groups on PDMS after each chemical treatment and on the final hydrogel coating formation was monitored using ATR-FTIR. The surface FTIR spectra of samples at each step of modification are shown in Figure 2. Compared with the pure PDMS surface, a broad peak of an O—H stretching vibration at around 3400 cm^{-1} appears in the spectrum of the oxidized form (Figure 2(b), left), indicating hydroxyl groups were generated on the surface after the oxidation process. These hydroxyl groups further reacted with TMSPMAs through silanization to present crosslinkable carbon−carbon double bonds on the PDMS surface. The characteristic absorptions at 1600−1660 cm^{-1} and 1660−1750 cm^{-1} (Figure 2(b), right) could be respectively attributed to the C═C stretch and C═O stretch of TMSPMA. Next, poly(ethylene glycol) (PEG) hydrogel coatings were fabricated and chemically adhered on the PDMS surface through direct crosslinking and with TMSPMAs. Curve D in Figure 2(a) is a typical FTIR spectrum of PEG hydrogel from crosslinked PEGDA macromers on PDMS substrates.[27] The peaks at 1096 cm^{-1} and 1730 cm^{-1} are respectively assigned to the C═O stretching vibration and the C—O asymmetric stretching vibration of C—O—C groups in PEG hydrogels. No obvious peaks of C═C groups around 1646 cm^{-1} were observed indicating the most of C═C groups in PEGDA macromers were consumed during the formation of the hydrogel coating.

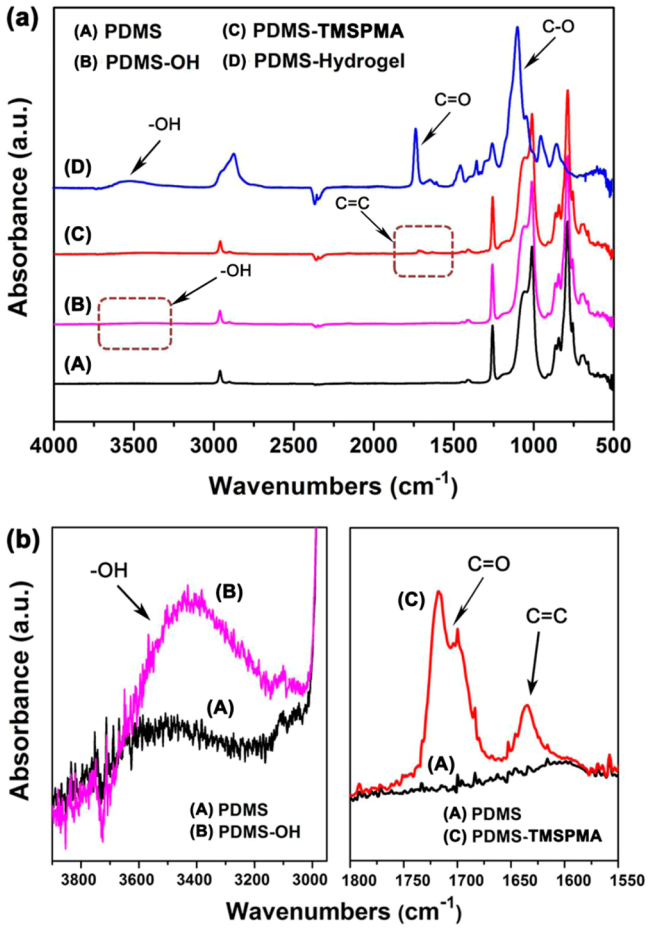

Figure 2. (a) ATR-FTIR spectra of (A) pure PDMS, (B) oxidized PDMS (PDMS−OH), (C) TMSPMA modified PDMS (PDMS-TMSPMA), and (D) PEG hydrogel coated PDMS (PDMS-Hydrogel); (b) partially enlarged ATR-FTIR spectra of pure PDMS, PDMS−OH, and PDMS-TMSPMA.

3.2. Morphology, Surface Adhesive Ability, and Wetting Property of Micropillar-Fixed Hydrogel Coatings on PDMS. Micropillar PDMS substrates with a pillar diameter of 22 μm, height of 66 μm, and inter-pillar spacing of 60 μm (i.e. center-to-center distance), were fabricated using a soft lithography method and then chemically modified. The morphology of the micropillar array and the hydrogel coating

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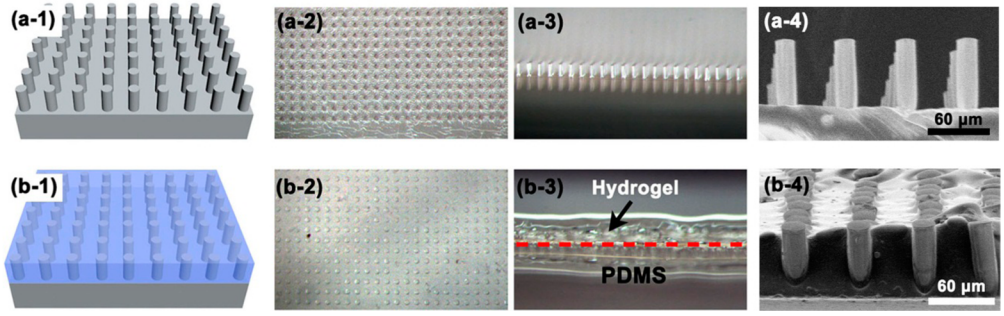

Figure 3. (a-1)−(a-4) PDMS with micropillars with hydrogel coatings and (b-1)−(b-4) PDMS with micropillars without hydrogel coatings. a2, a3, b2, and b3 are optical microscope images; a4 and b4 are SEM images.

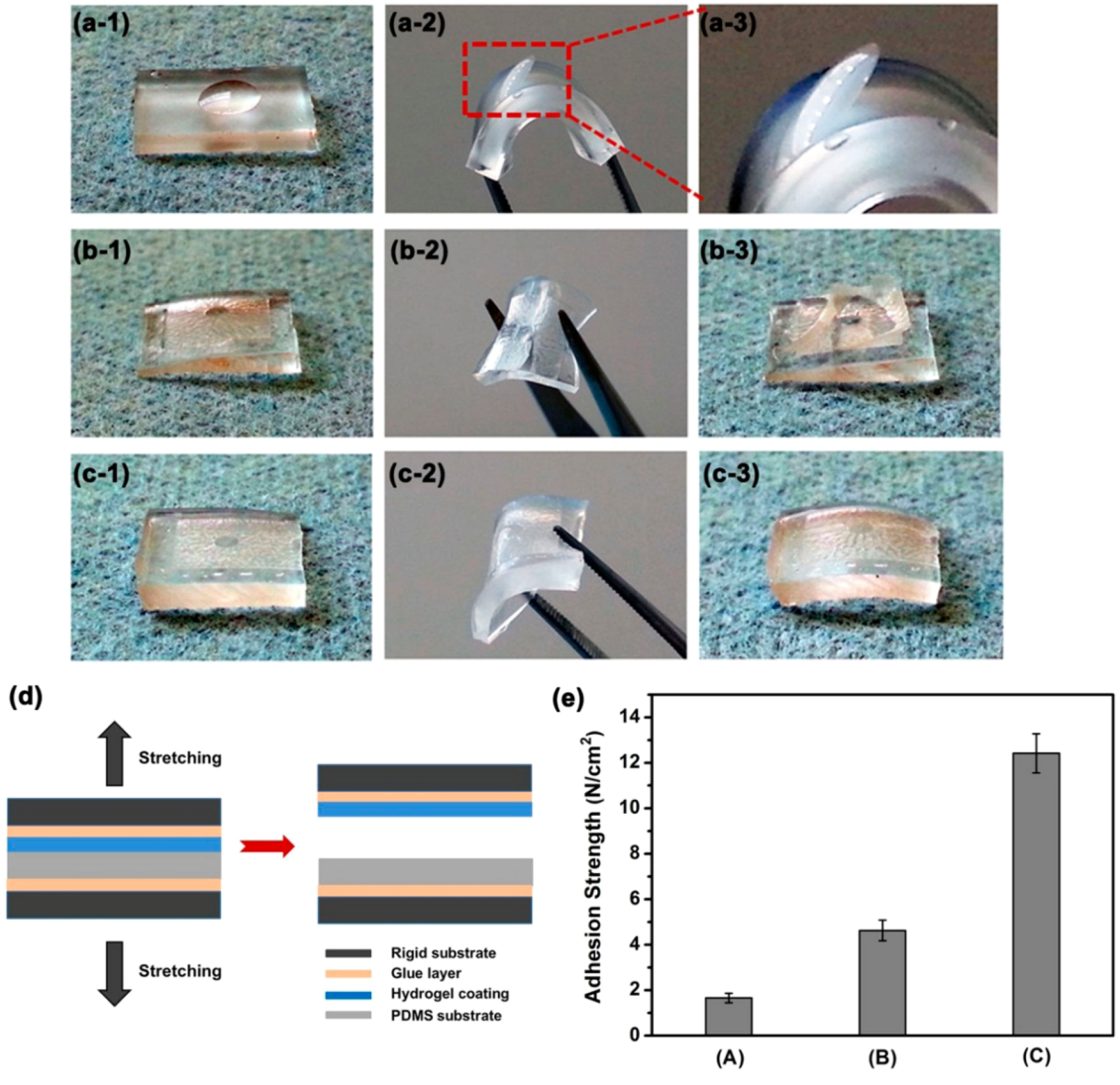

Figure 4. Adhesion evaluation of hydrogel coating on PDMS with (a) TMSPMA modification without micropillars, (b) micropillars but without TMSPMA modification, (c) micropillars and TMSPMA modification; (a2, a3, b2, and c2) coatings during blending tests; (b3 and c3) coatings after immersing in water; (d) illustration of the adhesion strength test of hydrogel coatings on PDMS; (e) the adhesion strengths of hydrogel coatings on different PDMS substrates: (A) flat PDMS with TMSPMA modification, (B) PDMS with micropillars but no TMSPMA modification, (C) PDMS with micropillars and TMSPMA modification. The error bars represent mean ± standard deviation (n = 4).

on PDMS substrates was observed by both OM and SEM (Figure 3). The OM images of the top view and the side view of micropillar array are shown in Figure 3 (a-2) and (a-3). A close-up SEM image of the side view is shown in Figure 3(a-4). The uniform micropillar array may help spread and hold the hydrogel precursor solution on the PDMS substrate to form a thin liquid film without additional spacers. Furthermore, such 3D micropillar arrays may increase the contact area between hydrogel solution and PDMS substrate comparing to flat PDMS surfaces and, consequently, increased covalent bonding

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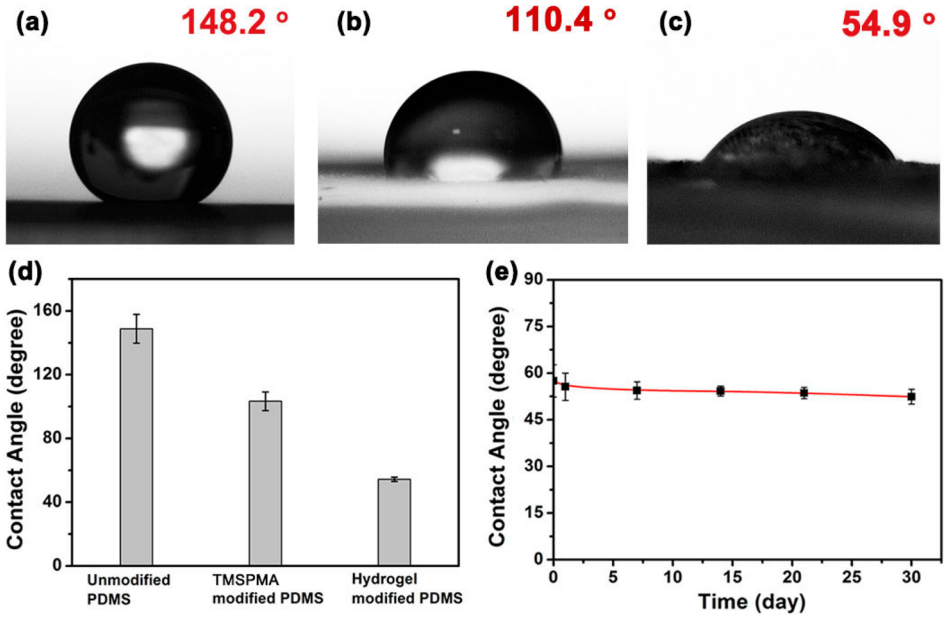

Figure 5. Water contact angles on (a) unmodified PDMS with micropillars, (b) TMSPMA modified PDMS with micropillars, (c) hydrogel modified PDMS, and (d) their comparison; (e) variation of water contact angle with time on hydrogel modified PDMS. The error bars represent mean ± standard deviation (n = 5).

sites, which helps to fix the hydrogel coating firmly on the substrate. We estimated that the surface area of a micropillar structured surface (with micropillars of diameter of 22 μm, height of 66 μm and inter-pillar spacing of 60 μm) is about 2.27 times greater than a flat surface. Further increases in the aspect ratio (micropillar height to cross section area ratio) or the density (number of micropillars per unit area) of the micropillar structure may increase surface area further but would be more challenging to microfabricate. The images of hydrogel coated PDMS substrates are shown in Figure 3(b-2)−(b-4). It can be seen that a continuous hydrogel coating was filled the spaces in the micropillar array and bonded tightly to the surface of PDMS substrate. As the SEM image was obtained in the dried state of the hydrogel coating, some top ends of the pillars can be observed due to the shrink of hydrogel coating, but there was no detachment of the hydrogel coating from the substrate.

To evaluate the adhesion between the hydrogel coatings and the micropillar PDMS substrates, hydrogel coatings were prepared on different PDMS substrates including (a) flat PDMS substrates with TMSPMA modification, (b) micropillar PDMS substrates without TMSPMA modification, and (c) micropillar PDMS substrates with TMSPMA modification. On the flat TMSPMA modified PDMS, the surface could not be properly wetted by the hydrogel solution because of the hydrophilicity of surface and surface tension of the hydrogel solution. The resulting hydrogel coating was uneven and easily detached when the substrate was bent (Figure 4(a-1)−(a-3)). On the PDMS substrate with micropillars but without TMSPMA modification, a uniform hydrogel coating was formed and could basically adhere to substrate when bending PDMS but failed to maintain any attachment with the substrate once being immersed in water for less than 1 min (Figure 4(b-1)−(b-3)). The detachment of the hydrogel coating from the PDMS substrate is due to the weak bonding between PDMS and the hydrogel, which could not resist the deformation of the hydrogel when the hydrogel coating swelled in water. On the PDMS with both micropillar array and chemical modification, no detachment was observed for the hydrogel coating when the substrate was bent or immersed in water (Figure 4(c-1)−(c-3)). The results indicate that both chemical modification and micropillar structuring are necessary for forming stable hydrogel coatings on PDMS. The chemically modified micropillar array helps the spreading of the hydrogel solution on the PDMS surface and also increases the covalent bonding sites to anchor hydrogel more firmly on the substrate. In addition to the bending test, a tensile test was also applied to the hydrogel coated PDMS substrates with micropillars to evaluate the adhesion properties of the coatings. The samples were stretched slowly and parallelly to the hydrogel coatings at a constant speed of 10 mm/min until failure. With the stretching of PDMS substrate, the hydrogel coating was fractured but still stayed attached to the PDMS even though the substrate was broken. The SEM images of the side view of the broken hydrogel coated PDMS substrate are shown in Figure S1 in the Supporting Information. No detachment of the hydrogel coating from the PMDS substrates was observed.

In addition, the adhesion strengths of hydrogel coatings on different PDMS substrates were quantified by de-bonding hydrogel coatings off from PDMS substrates (Figure 4(d)). The representative force-deformation curves obtained from the tests are shown in Supporting Information Figure S2. The adhesion strength of coatings shown in Figure 4(e) was measured based on the maximum force that separated the coating and the PDMS substrate. Obviously, the hydrogel coating on PDMS substrates with micropillar structure and chemical modification has the highest adhesion strength of about 12.4 N/cm^2. It is 7.4 times more than that of flat PDMS with chemical modification and 2.7 times that of PDMS with micropillars but no chemical modification. The hydrogel coating could remain stably attached to PDMS substrate during our experimental observation of more than three months.

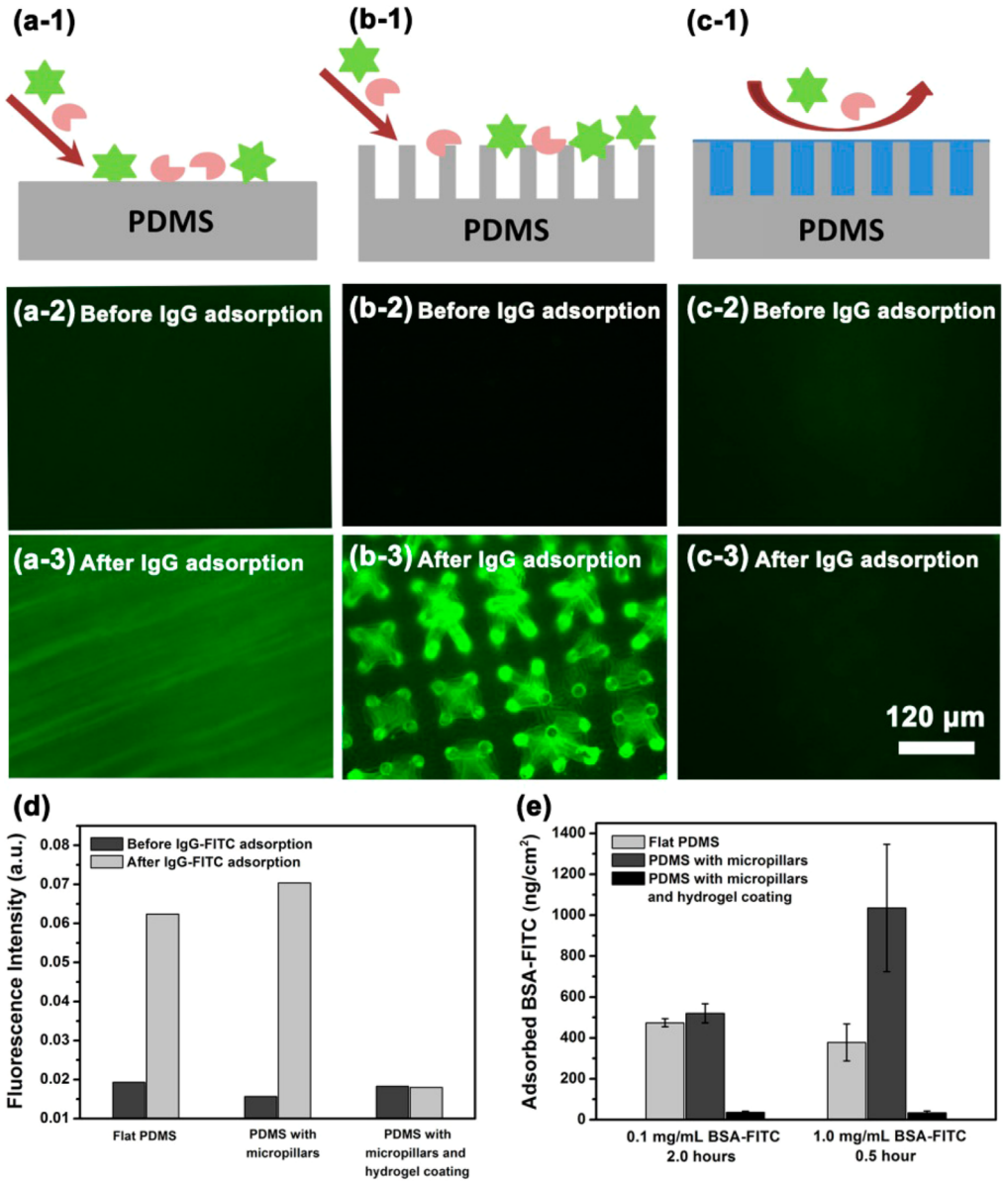

Figure 6. Protein adsorption on (a) flat PDMS, (b) PDMS with micropillars, and (c) PDMS with hydrogel coating; (d) the fluorescence intensity of IgG-FITC adsorption, which is denoted by of images of (a-2, a-3, b-2, b-3, c-2, and c-3); (e) the amount of BSA-FITC adsorption. The error bars represent mean ± standard deviation (n = 5).

Wettability of unmodified and modified PDMS was evaluated by measurement of water contact angles (Figure 5). Unmodified PDMS substrates with micropillar arrays exhibited high hydrophobicity with a CA of about 148°. After chemical modification, the CA was decreased to about 110°. The hydrogel coated PDMS substrates had a CA of about 55° and showed the most hydrophilicity, which could be maintained during our observation period of one month (Figure 5(e)). The enhanced wettability and prolonged hydrophilic durability of PDMA surface resulting from the introduction of hydrogel coatings could be very useful for PDMS based implants and devices in biomedical applications.

3.3. Protein Resistance Evaluation of Hydrogel Coatings on PDMS. To evaluate the protein resistance of hydrogel coated PDMS micropillar surfaces, FITC labeled IgG and BSA were used as model proteins. For IgG adsorption, 0.1 mg/mL FITC-IgG in PBS was applied separately on flat PDMS, micropillared PDMS and hydrogel coated PDMS. Fluorescence images were taken before and after exposure of different PDMS substrates to the IgG solution for 24 h and the fluorescence intensity of the images were compared (Figure 6(a)−(d)). For uncoated PDMS substrates, the fluorescence signal from adsorbed IgG (especially for the micropillar substrate with its increased surface area) was high due to significant protein adsorption. On the surface of hydrogel coated PDMS substrate, there was only a minor fluorescent signal indicating little protein adsorption. Furthermore, there was no variation of fluorescence intensity after 24 h incubation, which indicated that a long-term resistance to protein adsorption could be achieved using these hydrogel coatings.

For BSA adsorption experiments, 0.1 mg/mL of FITC-BSA with 2 h incubation or 1 mg/mL for 0.5 h incubation were investigated. The adsorbed BSA was detected using a microplate fluorometer and the amount of BSA adsorbed on different PDMS surfaces was quantitated using a standard curve method (Figure 6(e)). Hydrogel coated PMDS micropillar

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substrates showed the lowest BSA adsorption of about 35 ng/cm^2 in both adsorption conditions as compared to the other two unmodified PDMS substrates which had over 400 ng/cm^2 of BSA adsorption. The protein adsorption tests demonstrate that the hydrogel coatings can effectively resist nonspecific protein adsorption on PDMS substrates.

4. CONCLUSION

We have demonstrated the fabrication of a polymeric hydrogel coating on PDMS-based substrates using surface chemical modification on PDMS micropillar structures. The chemical modification with silane coupling agents provides PDMS surfaces with sufficient reaction sites to covalently anchor the hydrogel. Micropillar structures on the PDMS help increase the surface area to allow firm chemical adhesion between the hydrogel and the PDMS to withstand mechanical deformation of substrates and the swelling deformation of the hydrated hydrogel. In the study, the enhanced surface adhesion properties, long-term hydrophilicity, and the excellent protein resistance ability of the hydrogel coated PDMS were demonstrated. The proposed surface coating strategy may easily be extended to fabricating other hydrogel coatings on PDMS using different crosslinkable polymers, which may be very useful for engineering the surface of many PDMS-based devices to improve their biological performance.

■ ASSOCIATED CONTENT

Supporting Information

SEM images of the cross section of hydrogel coated PDMS substrates failed in a tensile test. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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