Lab on a Chip

Cite this: *Lab Chip*, 2012, **12**, 960

www.rsc.org/loc

PAPER

Polyurethane-based microfluidic devices for blood contacting applications

Wen-I Wu,[a] Kyla N. Sask,[b] John L. Brash[b] and P. Ravi Selvaganapathy*[a]

Received 4th November 2011, Accepted 3rd January 2012
DOI: 10.1039/c2lc21075d

Protein adsorption on PDMS surfaces poses a significant challenge in microfluidic devices that come into contact with biofluids such as blood. Polyurethane (PU) is often used for the construction of medical devices, but despite having several attractive properties for biointerfacing, it has not been widely used in microfluidic devices. In this work we developed two new fabrication processes for making thin, transparent and flexible PU-based microfluidic devices. Methods for the fabrication and bonding of microchannels, the integration of fluidic interconnections and surface modification with hydrophilic polyethylene oxide (PEO) to reduce protein adsorption are detailed. Using these processes, microchannels were produced having high transparency (96% that of glass in visible light), high bond strength (326.4 kPa) and low protein adsorption (80% reduction in fibrinogen adsorption *vs.* unmodified PDMS), which is critical for prevention of fouling. Our findings indicate that PEO modified PU could serve as an effective alternative to PDMS in blood contacting microfluidic applications.

Introduction

PDMS has been widely used in microfluidics for rapid prototyping because it is easy to fabricate, it bonds strongly to glass and PDMS substrates, and has good optical transparency and elastomeric properties. However, its intrinsic hydrophobic nature causes significant protein adsorption from protein-containing fluids. Proteins are in general amphiphilic molecules, containing both hydrophilic and hydrophobic regions. Blood contains various plasma proteins at different concentrations and with different surface affinities. Fibrinogen, an abundant plasma protein involved in blood coagulation, has been found to adsorb significantly more on hydrophobic than on hydrophilic surfaces.[1–3] The adsorption of fibrinogen potentiates the process of thrombosis including platelet adhesion and fibrin (clot) formation. A number of attempts have been made to reduce protein adsorption on PDMS surfaces and microchannels as summarized in recent reviews. The surface modification of PDMS can be difficult due to the absence of surface functional groups and the complex processes needed to introduce appropriate chemical functionality. Plasma,[4–7] UV irradiation[8–10] and gas phase modification[11–13] have been used to make PDMS surface hydrophilic. However, these modifications are temporary and the surface was found to ultimately revert back to the hydrophobic state due to loss of the modifier.[14,15] Other methods are based on covalent attachment of surface groups through chemical modification. While attachment chemistries use organic solvents that swell PDMS[16] and are typically performed on open surfaces that cannot be bonded to other substrates[17] to form channels, aqueous-based modification[18] avoids this problem and was successfully implemented inside microchannels[19,20] showing some resistance to lysozyme and bovine serum albumin. However a recovery of surface hydrophobicity was reported due to the migration of PDMS molecules and the elution of grafting polymers.[19]

Polyurethanes (PU), since their development in the 1930s,[21,22] have been widely used in various blood-contact applications such as the artificial heart,[21] intra-aortic balloons,[23] pacemaker leads,[24] heart valves,[25] and hemodialysis membranes.[26] Hydrophobic surfaces are essentially water repellent and provoke adverse reactions in blood contact. Many studies have shown that the blood compatibility of polyurethanes can be improved by making the surface more hydrophilic.[27] A number of *in vivo* and *in vitro* studies have been carried out to assess the cellular and tissue responses of PU either subcutaneously, intramuscularly, or intraperitoneally.[28–37]

A very important consideration for hemocompatibility and biocompatibility is protein adsorption. In blood contact, for example, plasma proteins including albumin, hemoglobin, thrombin, fibrinogen (Fg), fibronectin, complement components, and immunoglobulins (IgG) adsorb onto polymeric surfaces immediately. Adsorbed fibrinogen in particular has been shown to be associated with thrombus formation. It has been suggested that blood compatibility may be improved by controlling interfacial interactions such that non-specific protein adsorption is prevented while selective adsorption of proteins for a desired bioactive function is promoted.[38] Approaches to limiting

[a]*Department of Mechanical Engineering, McMaster University, JHE-212/B, 1280 Main Street West, Hamilton, ON, Canada L8S 4K1. E-mail: selvaga@mcmaster.ca; Fax: +1 905 572 7944; Tel: +1 905 5259140 ext. 27435*
[b]*School of Biomedical Engineering, McMaster University, CRL-230, 1280 Main Street West, Hamilton, ON, Canada L8S 4K1. E-mail: brashjl@mcmaster.ca; Fax: +1 905 572 7944; Tel: +1 905 5259140 ext. 24946*

non-specific adsorption include modification of the surface with hydrophilic polymers such as polyethylene oxide (PEO) and poly(2-methacryloyloxyethyl phosphorylcholine) (poly-MPC).[39–41] Photo-chemical reactions[42,43] and various grafting techniques[44,45] have been used for this purpose. PEO is well known for its protein and cell resistant properties and different methods for generation of PEO-rich surfaces include adsorption, blending and grafting.[46–51] Although various methods for surface modification exist, such modification has been demonstrated on open surfaces or films of PU and not inside microfluidic channels. Surface modification inside microchannels present a different set of challenges, such as rapid depletion of reagents due to high surface to volume ratio that the modification chemistry has to take into account.

Traditionally, solvent moulding techniques such as vertical dipping, rotating mandrel and rotating plate are used to fabricate PU parts such as sheets, membranes and tubing. The rotating plate method is used for fabricating PU films and sheets, while vertical dipping and rotating mandrel are used for fabricating cylindrical parts, like tubing. However, these fabrication techniques are not suitable for replicating the intricate and detailed microscale features present in microfluidic devices. PU-based microfabrication typically involves injection moulding,[52,53] hot embossing,[54] imprinting,[55] plasma etching,[56] sacrificial material[57] and reaction polymerization.[53,57–60] These methods are not suited for rapid prototyping as they use high-cost intermediate moulds and expensive fabrication equipment. Furthermore, the substrates produced are rigid and not transparent. Solvent casting is more suitable since intermediate moulds can be fabricated using photolithography and the fabrication equipment is low cost. However, the substrates that are produced are opaque, do not bond well and are difficult to connect with tubing.

Here, we report on a method for fabrication of PU, similar to methods used for PDMS but leading to devices having hydrophilic interior surfaces. This method potentiates PU as an effective alternative to PDMS in many biological and biomedical microfluidic applications. We also develop several effective bonding and interconnection methods for solvent cast PU microfluidic networks to produce PU elastomeric devices that could be rapidly prototyped. In the work reported here we developed an *in situ* surface modification method to graft PEO to PU surfaces in the interior of moulded and sealed microfluidic channels. The procedure is adapted from a previously published method.[61] Resistance to biofouling of the surface modified devices was assessed by measuring the adsorption of fibrinogen. Adsorption to devices fabricated using PDMS and unmodified PU was measured for comparison.

Experimental details

Materials

The polyurethane Tecothane® TT-1095A was from Thermedics® Polymer Products (Wilmington, MA). SU-8 photoresists including SU-8 100, SU-8 2000.5, SU-8 2007, SU-8 2015, and SU-8 2025 and single-side polished mechanical grade silicon wafers were from Microchem Co (Newton, MA) and University Wafer (Boston, MA) respectively. Polydimethylsiloxane (PDMS) Sylgard® 184 was from Dow Corning (Midland, MI). N,N′-dimethylacetamide (DMA), dimethylformamide (DMF), tetrahydrofuran (THF), methylene chloride, cyclohexanone, chloroform, triethylamine (TEA, 99%), anhydrous toluene, chloroform, dimethyl sulfoxide (DMSO), xylene, 1-propanol, ethyl alcohol, cyclohexane, acetone, isopropyl alcohol (IPA), ethyl ether, methanol, N-hexane, glycerol, formaldehyde and anhydrous acetonitrile were from EMD Chemicals (Gibbstown, NJ) and were used as received. 4,4′-Methylene-bis (phenyl-diisocyanate) (MDI) and dihydroxy polyethylene oxide (PEO, MW = 1000) were from Sigma Aldrich (Oakville, ON). Human fibrinogen was from Enzyme Research Laboratories (Southbend, IN). Masterflex® peroxide-cured silicone and Masterflex® Tygon® tubing were from Cole-Parmer (Vernon Hills, IL).

Solvent casting process

Solvent casting involves the formation of a replica by pouring the casting solution (prepared by dissolving polymer in solvent) into the mould. After curing (removal of solvent), a solid replica is created that can be removed from the mould. The mould can be used multiple times making the cost of the parts substantially cheaper. An important criterion in the choice of the mould material, the polymer and the solvent is that the casting solvent should dissolve the polymer completely but not dissolve or otherwise alter the mould at all.

In this study, we chose patterned SU-8 photoresist on single-side polished mechanical grade silicon wafers as the mould material due to ease of fabrication and resistance to the casting solvent. Various SU-8 photoresists such as SU-8 100, SU-8 2000.5, SU-8 2007, SU-8 2015, and SU-8 2025 were used to obtain a wide range of feature sizes.

Tecothane® aromatic polyether-based thermoplastic is a medical-grade polyurethane with good chemical resistance and biostability and has been used in many implantable medical[62–64] and healthcare applications.[65–67] It is licensed for long-term usage and has passed USP Class VI.[64] This material has been tested extensively in clinical practice. It has density (1.15 g/cc) and melting point (215.5 °C) similar to PDMS. Its mechanical properties are superior, namely higher tensile strength (62 MPa), Young's modulus (55 MPa) and hardness (94 Shore A). Its dielectric constant is similar to that of PDMS and it performs well as an insulator. Tecothane® was chosen as a model material in this study due to its excellent properties and ready availability. Various organic solvents including dimethylacetamide, dimethylformamide, tetrahydrofuran (THF), methylene chloride, cyclohexanone and chloroform were tested for their ability to dissolve Tecothane® and for their compatibility with SU-8. THF was chosen since it dissolves PU readily, can be rapidly removed by evaporation at room temperature and leaves SU-8 mould intact after repeated cycles while other solvents either partially dissolve or swell SU-8 after curing. The PU "resin" is prepared by dissolving Tecothane® pellets in THF. A concentration of 10% (w/v) was found to be optimal for fast curing, high transparency and surface smoothness. The solution was prepared by stirring for 3 h at room temperature.

To achieve a robust, flexible and cost-effective interconnection, a solvent based method was developed. This method is suitable for any material that is soluble in THF. Two common tubing materials, silicone and Tygon® tubing, were investigated

due to their reasonable solvent resistance and biocompatibility. Typically, Tygon® tubing provides higher pressure tolerance, lower gas permeability, and better chemical resistance than silicone tubing while the latter is relatively cheap.

Fabrication process

The casting based fabrication process for PU microchannels is shown in Fig. 1. The PU solution is cast directly on the SU-8 mould. After curing for 60 min, fluidic interconnects (φ3 mm Tygon® or silicone tubing) are placed manually on top of the inlet and outlet reservoirs on the mould and fixed in place using PU solution as a glue. After curing for another 10 min, the patterned PU film with integrated interconnects is peeled off the mould and subsequently bonded to another flat PU film or glass substrate.

Moulding process

The moulds were made with SU-8 photoresist by conventional photolithography (Fig. 1). The thickness of the SU-8 moulds ranged from 0.5 μm to 80 μm. The PU solution was cast on the moulds (Fig. 1(c)). Although solvent casting has been used to form PU thin films less than 50 μm in thickness[68] using THF as solvent, this method is not suitable for fabricating microchannels in thick films with intricate features for several reasons. First, THF is a solvent for many polymeric materials. Therefore, moulds have to be made of glass, silicon, ceramic materials or photoresists covered with electroplated metal layers[58] making them expensive and difficult to fabricate. Second, when thick films of PU are formed using THF as solvent by curing in ambient conditions (Fig. 2(a)), small microscopic cavities may be present (Fig. 2(b)). These cavities are formed by the rapid transport of the solvent, enabled by its high vapour pressure (143 mmHg), from the top layer of the thick film surface, into the atmosphere. Subsequently the spaces that are originally filled with THF become cavities or voids. This rapid transport causes the interface with air to dry faster compared to the bulk, leading to solvent trapping which upon evaporation leads to cavity formation.

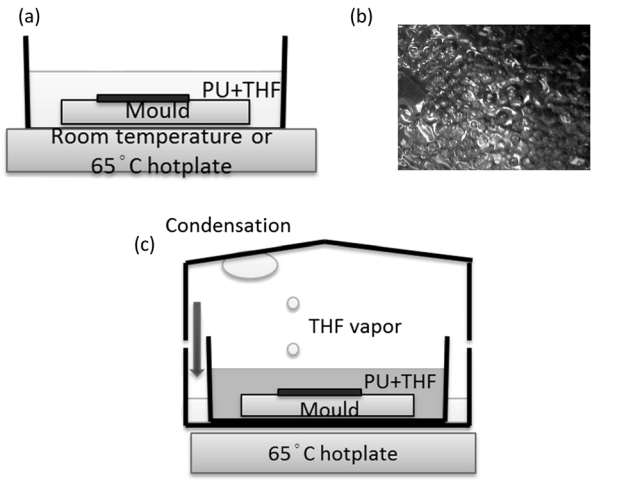


Fig. 2 (a) General setup for solvent evaporation; (b) air voids and pockets trapped in PU; (c) dedicated setup for solvent evaporation without causing voids.

The experiments with the different solvents showed that SU-8 is an ideal low-cost, photolithographically definable mould material for casting polymers dissolved in THF. Fully cured SU-8 had negligible dissolution in THF even with multiple castings. In order to mitigate cavity formation, the curing process was performed in a closed chamber, where the vapour pressure quickly reaches saturation and the curing process is slowed. Although this modification eliminated cavity formation, the time to completely cure a film 1 mm in thickness took longer than 12 h, making the method impractical. Consequently, a controlled evaporation method was developed using the setup shown in Fig. 2(c). Here, the evaporation process is accelerated by heating the substrate to 65 °C. The vapour pressure is maintained close to saturation by enclosing the substrate in a chamber. This "saturated" chamber prevents the hardening of the top layer and eliminates voids in thick films. Excess THF is allowed to condense and fall to the side. Using this setup, the curing process

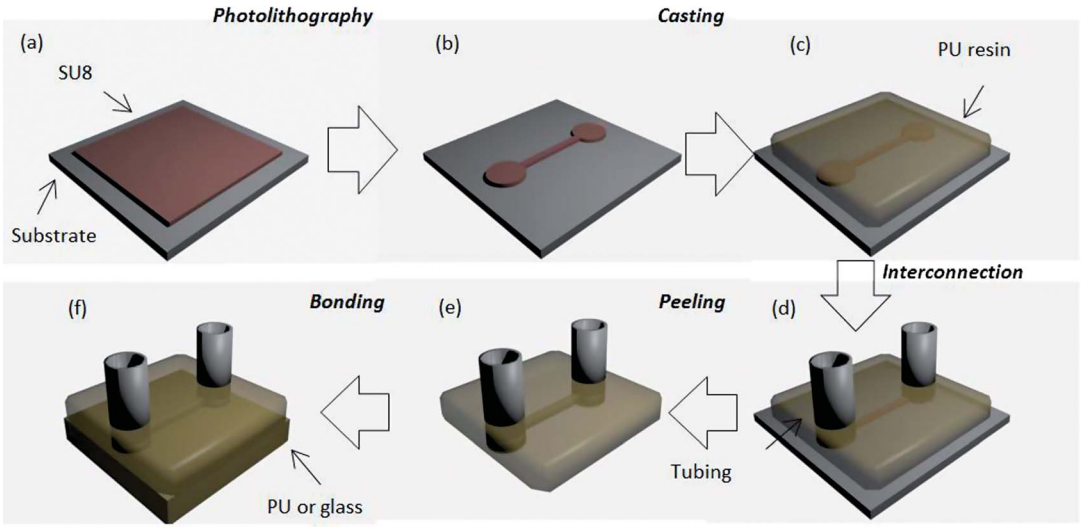


Fig. 1 Process flow of PU soft-lithography.

is complete within 1 h producing a smooth, transparent PU replica. While the surface features of the replica are determined by the mould, the thickness can be controlled by regulating the volume of PU solution. In our experimental setup, a 50 μm-thick PU replica was obtained by casting 10 mL of 10% (w/v) PU solution into the moulds made from SU-8 patterned 3″ silicon wafers and placed in glass petri dishes.

Interconnection

Reliable and leak-proof fluidic interconnects capable of withstanding high pressures are critical for microfluidic devices. Common methods include the use of adhesives,[69,70] o-rings,[71,72] Mylar polymer sealants,[73] molten plastic tubing tips,[74] mechanical compression,[59,75–77] and commercial connectors such as Upchurch Scientific's Nanoport™ and LabSmith's CapTite™. While most commercial connectors provide fast assembly, tolerance of high pressure, and reliable interconnection, customized port design is required for microfluidic devices and the cost is high. The use of adhesives can be implemented easily but there is a risk of clogging if the adhesive seeps into the microchannels during application. Moreover the bonding strength varies depending on the material of the tubing and device. Use of adhesives and O-rings may lead to sample contamination especially if they are attacked by solvents and chemicals used in the device. An alternate low cost, reliable method is to use a solvent that dissolves the substrate and the interconnect thus re-enforcing the material at the interconnect and forming a strong, stable bond. This method, known as solvent welding, is commonly used for connecting plastic tubing such as polycarbonate, polystyrene, PVC and ABS and has been used to seal polymeric microfluidic devices using low boiling azeotropic solvents.[78,79] No foreign material is introduced after the solvent is evaporated and thus there is no contamination and the risk of catastrophic failure is low. Among the various solvents used in this work, THF was found to dissolve not only PU but also other materials such as silicone and Tygon® tubing.

In initial experiments, pure THF was used to partially dissolve the surfaces to be bonded, ie the PU replica and the tubing. The tubing was then placed on the PU surface and allowed to cure. Bonding occurred as the two materials "fused" and no fitting was required. However, since the evaporation of THF was rapid, the bond formed was relatively weak. In subsequent experiments, a solution of PU in THF (10% w/v) was applied to the regions on the PU replica and the tubing that were to be connected. The evaporation process was slower and produced a stronger bond between the interconnect tubing and the PU replica. The tip of the tubing was dipped into the PU solution and then aligned with the reservoir of the PU replica as shown in Fig. 3(a). The combination was either left at room temperature for 30 min or on a hot plate at 65 °C for 10 min to fully cure as shown in Fig. 3(b). Subsequently, the cured PU replica with integrated interconnects was peeled from the mould as shown in Fig. 3(c). Punch tools with φ3 mm cutter tips were used to remove residual PU inside the tubing as in Fig. 3(d). The only limitation of this method is the size of the tubing as it becomes difficult to align and hold the tubing in position on the mould and clean residual PU inside it. Tubing with an inner diameter of 3 mm and a length of 25 mm was used in this study.

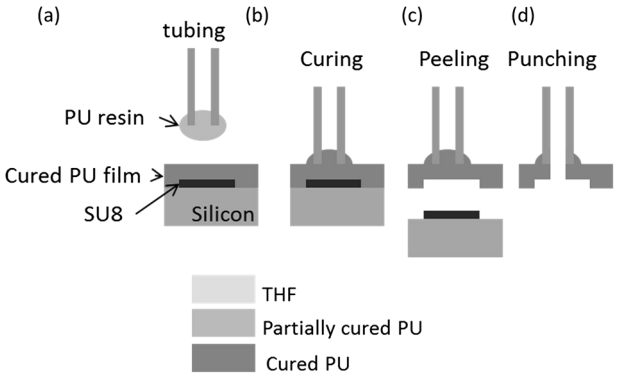


Fig. 3 Interconnection procedure: (a) dip-coat partially cured PU on the tip of tubing; (b) place tubing on top of the inlet and outlet reservoirs on the mould and complete the curing process; (c) manually peel the pattern PU film with integrated interconnects; (d) remove residual PU from inside the inlet and outlet using punch tools.

Bonding methods

A major advantage of PDMS micromoulding that has made it the most popular rapid prototyping method in microfluidics is the ability to form a strong irreversible bond with glass or PDMS through a simple process of exposure to oxygen plasma. The bond formed is strong and can withstand significant pressure. For other polymers like poly(methyl methacrylate) (PMMA), polycarbonate (PC), polystyrene, cellulose acetate, and poly(ethylene terephthalate), the most common method is lamination to the other polymeric film with pressure sensitive adhesives,[80] thermally-activated adhesives[81,82] or intermediate layers such as parylene.[83,84] In the adhesive methods, the bonding surface is wetted by the adhesive thus giving a strong bond. However they are susceptible to dissolution by solvents that may be used in the device and could cause contamination and failure. In the case where intermediate layers are used, high processing temperature or plasma treatment with specific gas species is required.

A similar, simple bonding method for PU does not exist. Semi cured parts of PU have been placed in contact and heated above the glass transition temperature causing fusion of the two parts.[53,58] However, this method is not suitable for retaining the fine structural features needed in microchannels.

In this work we developed several new methods for bonding PU parts with detailed microstructural features to other PU films. These methods can be categorized as dry and wet. Wet bonding methods include the use of dip coating and micro contact printing[60,85] and are suitable for high aspect-ratio channels. In this method, a flat PU film is either dipped vertically into pure THF solution for approximately 10 s to avoid excessive dissolution of the PU (dip coating, Fig. 4(a)), or spin-coated with a solution of PU in THF (10% w/v) at 100 rpm for 10 s to avoid rapid solvent evaporation that occurs by convection at high rpm (micro-contact printing, Fig. 4(b)). In the former method, the PU surface is partially dissolved by THF, retains some solvent and becomes adhesive. The microstructured PU layer is then placed on top of this partially dissolved PU film. In the latter method, the microstructured PU layer is stamped on the spin-coated wafer to transfer the PU resin from the wafer to the PU layer and then placed on top of another dry PU film. The combination is

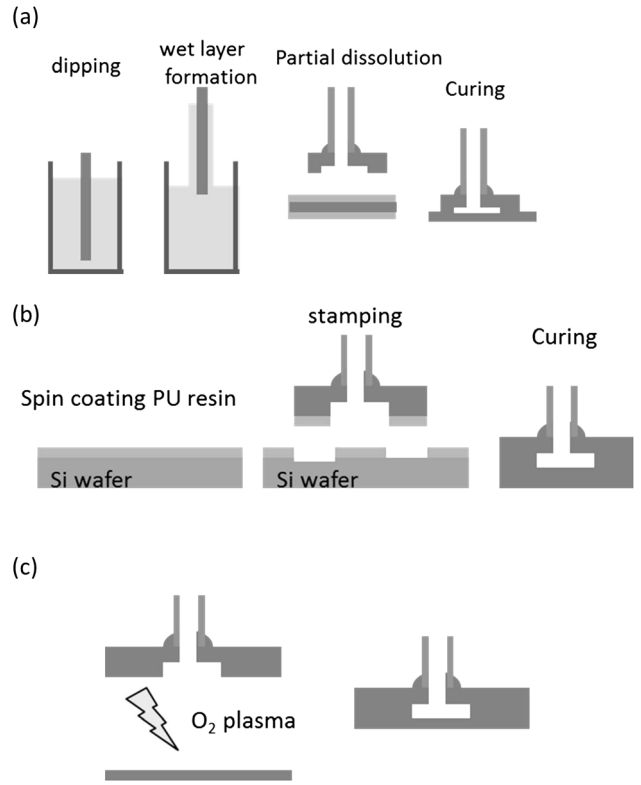


Fig. 4 PU bonding. (a) Dip coating; (b) micro contact printing; (c) oxygen plasma treatment.

transferred to a hotplate and cured at 65 °C for 10 min. Both methods are suitable for microchannels but not for nanochannels as the THF and PU resin will destroy any nanostructural features that are present. As an alternative, dry bonding of PU microstructured layers with PU films or glass using oxygen plasma was also investigated and used to fabricate nanochannels of height <1 μm. In this method, patterned and flat PU pieces or glass substrates were treated by oxygen plasma at 60 W for 1 min as shown in Fig. 4(c) and then placed together under pressure (~1 kg) for 4 h to achieve stronger bonding. Similar procedures have been used for PDMS to improve the bond strength.[86]

Surface modification

Attempts were made to improve resistance to protein adsorption by grafting poly(ethylene oxide) (PEO). Previous work[46–51] on attachment of PEO to PU used methods adapted for flat films and were found not to be suitable for microfluidic channels. The extent of surface modification was minimal probably due to high surface to volume ratio of the microchannels which leads to rapid depletion of the reactants. Therefore, a two-step process (Fig. 5), based on previously published protocols,[61] was adapted to graft PEO to PU microfluidic devices; typical device dimensions were 1 cm × 1 mm × 80 μm. First, a solution of 4,4′-methylenebis(phenyl isocyanate) (MDI) in anhydrous toluene (7.5%, w/v) containing 2.5% (w/v) triethylamine (TEA) as catalyst was heated to 50 °C under a stream of nitrogen. Meanwhile, the PU-based microfluidic devices were dehydrated in a vacuum oven and then preheated to 70 °C. The MDI solution (50 °C) was then infused into the device with inlet and outlet sealed to prevent evaporation. The MDI solution was refreshed every 30 min. After 2 h, the devices were rinsed with anhydrous toluene and immediately infused with 7.5% (w/v) monomethoxy-poly(ethylene glycol) (MeO–PEO–OH) in toluene and reacted for 24 h at 40 °C. The devices were rinsed with water to remove unreacted PEO and dried under vacuum overnight at 40 °C.

Measurement of protein adsorption

The adsorption of fibrinogen from buffer was measured using ^{125}I-labelled protein. Fibrinogen was labelled using the iodine monochloride method.[61] Free iodide was removed on AG 1-X4 resin. Residual free ^{125}I-iodide was determined using the trichloroacetic acid precipitation method and levels were kept below 1%. The solution for adsorption experiments consisted of 2% labelled and 98% non-labelled protein in phosphate buffered saline (PBS) at a total concentration of 1 mg mL^{-1}. The devices were incubated in PBS at room temperature for 2 h prior to exposure to the radiolabelled protein solution which was then infused *via* syringe. Adsorption was allowed to proceed for 3 h at room temperature. Following adsorption, the devices were rinsed 3 times (10 min each time) with PBS. Samples of the microchannels 6 mm × 1 mm × 80 μm (surface area of 0.13 cm^2) were punched from the devices and placed in counting vials for radioactivity determination using a γ-counter (Wizard 1480 – Perkin-Elmer). Unmodified PDMS, unmodified PU and PU-PEO microfluidic devices and φ6 mm films were used in these experiments.

Results and discussion

Polyurethane replica characterization

Our modified experimental setup (Fig. 2(c)) reduced the curing time to ~1 h by heating the mould to 65 °C. The moulds had patterns for 10 microchannels in parallel between the inlet and outlet reservoirs and the channels had length and width of 1 cm × 150 μm and heights of 500 nm to 80 μm depending on the photoresist. The PU replicas as peeled from the mould appeared smooth and transparent. Images of the fabricated PU microchannels were obtained by scanning electron microscopy (SEM, Hitachi S-2150) (Fig. 6). It can be seen that very good replication of the patterns in the SU-8 mould was achieved. The top and bottom surface appear very smooth while the sidewalls are straight and rough. The roughness of the side walls is due to the low resolution (10,160 DPI) transparency masks (Fine Line Imaging Co) used in the photolithography process and is observed in the SU-8 mould as well. The replication of striations on the sidewalls from the mould to the PU replica indicates that fine sub micrometre features can be replicated using this solvent casting process. To determine whether sub-micron channel sizes could be fabricated using this method, a mould with 500 nm high channels was used. The cross-sectional profile and surface roughness of the PU replica thus formed were measured using white light interferometry (Zygo NewView 5000, Zygo Corporation, CT). The cross sectional profile confirms that 500 nm size microchannels can be replicated easily using this method.

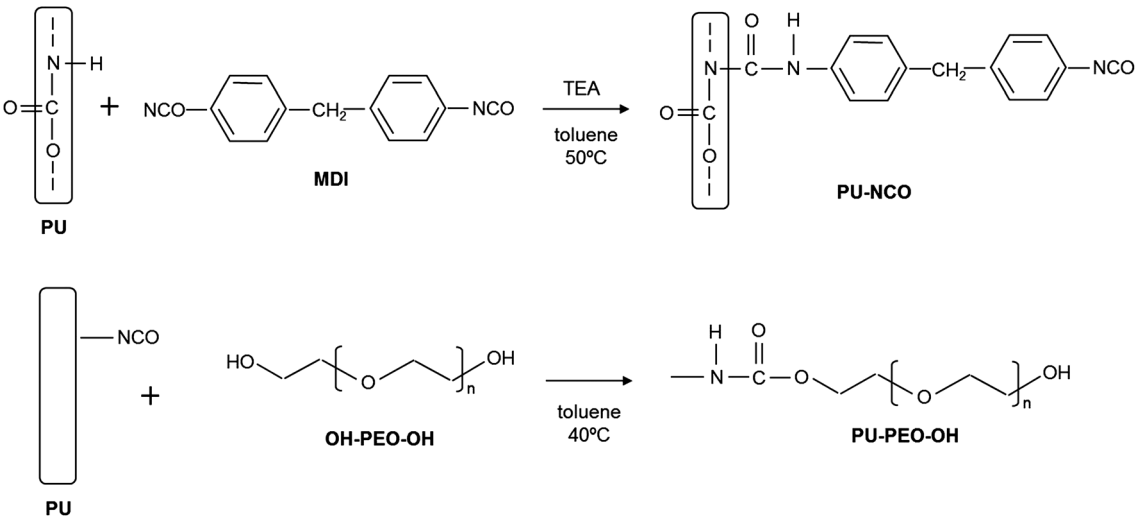


Fig. 5 PU surface modification with PEO.

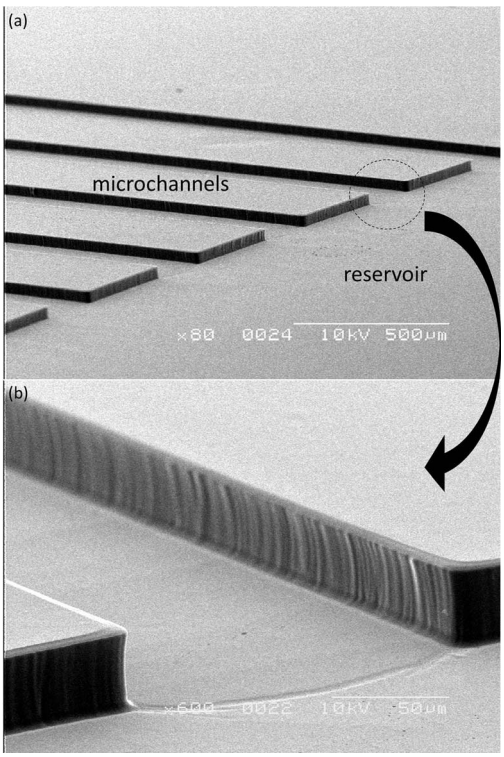


Fig. 6 SEM of a microfluidic device with 10 microchannels in parallel between inlet and outlet reservoirs. (a) Unsealed PU replica (45 μm high), (b) high magnification view of the bottom and side wall surfaces in the microchannel.

This result suggests that the surface roughness on the replica can be further reduced using photoresists with smoother surfaces and masks of better quality. The SU8 mould was used a number of times (≥10) without any damage or deterioration. The appearance of sealed devices is showed in Fig. 7(a).

Optical transparency is crucial in microfluidic devices, especially for prototyping applications. The replicas prepared by casting produce optically transparent films as shown in Fig. 7. To investigate light transmission, measurements were performed on 500 μm thick PU films (Beckman DU640 UV-vis spectrophotometer) in the wavelength range from 200 to 800 nm. A 150 μm thick cover glass slide (VWR No.1) was used as control. The average transmission of the PU film in the visible region (390–750 nm) was above 85%; it absorbed strongly in the near-UV region (300–400 nm). Absorption in the near UV is associated with the bonds in the polymer itself and causes photodegradation with gradual change in color (yellowing),[87] which is commonly seen in thermoplastics. The surface wettability of PU formed by solvent casting was determined by water contact angle (KRÜSS DSA100 goniometer) and compared to PDMS and glass. Samples were kept in ambient air for 2 days prior to measurement. The borosilicate glass slides were cleaned

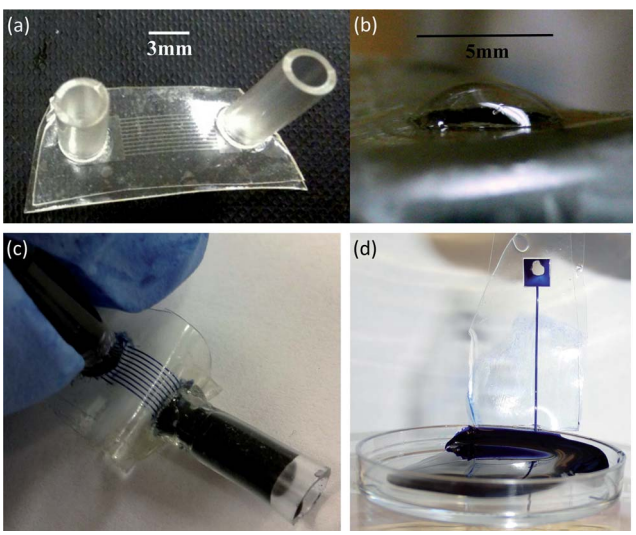
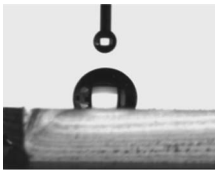
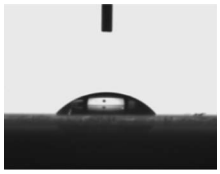


Fig. 7 Photos of PU-based microfluidic devices. (a) Sealed device with integrated interconnect, (b) a deflected PU membrane under a pressure of 200 kPa (φ5 mm and thickness = 25 μm), (c) a flexible and bendable device with coloured microchannels for visualization, (d) self-priming microchannel (4 cm × 500 μm × 80 μm) filled with DI water (dyed with methylene blue) due to its hydrophilicity.

Table 1 Contact angle measurements (4 μL DI water drops)

PU 63.0 ± 1.38°	PDMS 112.9 ± 4.8°	Glass 51.2 ± 1.33°
		

with acetone, methanol and DI water, and dried before testing. The results, reported in Table 1, show that unmodified PU was significantly more hydrophilic ($\theta = 63°$) than PDMS ($\theta = 113°$) and less hydrophilic than glass ($\theta = 51°$). The angles did not change significantly after two more days in ambient air. Its hydrophilicity can facilitate the priming process without applying pressure into the microchannels. As depicted in Fig. 7(d), an unfilled PU microchannel was placed vertically and dipped into DI water dyed with methylene blue, and immediately the microchannel was self-priming by the capillary flow.

Disks of PU (φ6 mm) were immersed in dimethylformamide (DMF), tetrahydrofuran (THF), chloroform, dimethyl sulfoxide (DMSO), xylene, 1-propanol, toluene, ethyl alcohol, cyclohexane, acetone, isopropyl alcohol (IPA), ethyl ether, acetonitrile, methanol, N-hexane, glycerol, formaldehyde, and DI water for 24 h. The diameters of the disks were measured and analyzed (IMAGEJ® software) before and after immersion, with swelling ratio defined as $S = D/D_0$ (D diameter after 24 h in solvent, D_0 diameter of dry disk). As seen in Fig. 8, THF and DMF dissolved the PU; only chloroform and DMSO gave S >1.1. The swollen PU returned to its original shape after removal of the solvent. With DMSO, however, the PU was transformed into a white gel. These results demonstrate that PU is compatible with most solvents except THF and DMF, and in general swells less than PDMS[16] which has S = 1.39 for chloroform, 1.41 for xylene, 1.33 for cyclohexane, and 1.31 for toluene.

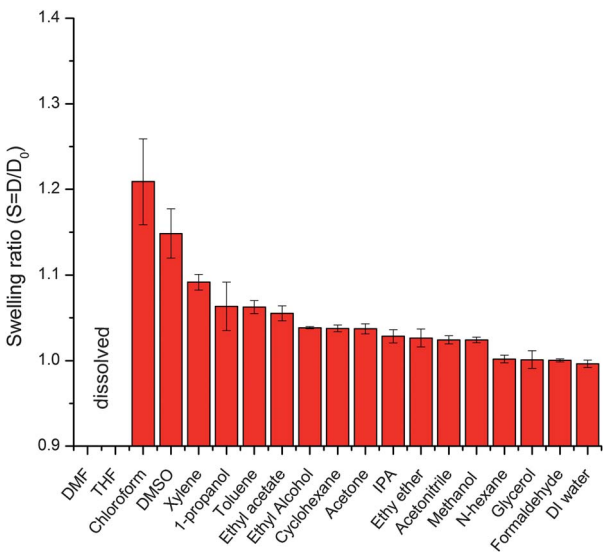


Fig. 8 Solvent compatibility based on the swelling ratios of PU after 24 h immersion. Data are means ± SD, n = 5.

Characterization of sealed PU microfluidic devices with integrated interconnection

Using the solvent seal method shown in Fig. 3, Tygon® was used as interconnect tubing since it has higher pressure tolerance than silicone. The combined interconnect and microchannel relief was bonded to a thin PU film to seal the microchannel. Since the surfaces on the PU replica and the tubing were partially dissolved by THF, a strong bond was expected to form. Fig. 9(a) shows a SEM cross section of the bonded region where the Tygon tubing interfaces with the PU microchannel. It can be clearly seen that the bottom PU film, the top PU film and the Tygon tubing merge with one another. No clear interface can be seen indicating formation of a strong bond. Burst tests were conducted by sealing the outlet interconnect and applying increasing pressure on the inlet. Failure at the interconnect-PU interface was not observed up to 375 kPa pressure. At higher pressure the fitting connecting the pressure sensor to the device leaked.

The various wet and dry bonding methods shown in Fig. 4 were evaluated for pressure resistance. A cross section of the channels formed by PU films patterned with microchannels bonded to flat PU thin films using micro-contact printing (Fig. 4(b)) is shown in Fig. 9(b), (c) and (d). It can be seen that the rectangular cross section of the channels was preserved in the micro-contact bonding process. Furthermore, no clear interface can be seen between the top and bottom PU film indicating that

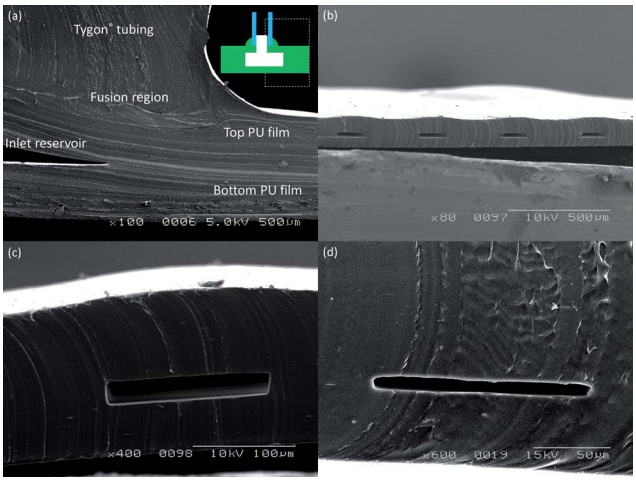


Fig. 9 SEM images of (a) the bonding interface of Tygon® tube and PU film (b) cross-section of sealed PU channels formed by μcontact printing, (c) 35 μm high sealed PU channel (zoomed view) and (d) high-aspect ratio PU sealed channel, 10 μm high × 150 μm wide (zoomed view).

fusion of the material at the interface is good with strong bonding expected. One notable feature of PU is its high Young's modulus which allows micro-contact printing and bonding of thin films while still preserving the integrity of the microchannels. Channels such as those shown in Fig. 9(d) (10 × 150 um cross section) with thin top and bottom films would collapse during micro-contact printing and bonding if made from PDMS. The ability to fabricate extremely thin microfluidic devices allows the device to be much more flexible and bendable as shown in Fig. 7(b)(c) and (d) therefore useful in applications where rolling is needed.

The burst pressures of sealed PU microfluidic devices with integrated interconnects fabricated by various bonding methods were determined. Water was infused through the Tygon® interconnect at a flow rate of 1 mL min^{-1} *via* a syringe pump (Harvard Apparatus, Holliston, MA), and the outlet of the microfluidic device was connected to a pressure sensor (Omega PX273-300DI). The pressure within the device was recorded. Data are shown in Table 2. For each bonding method 5 replicate burst tests were performed and the average values are reported. Dry bonding involving activation of the PU surfaces in oxygen plasma (60 W, 1 min) gave a burst pressure of 42 ± 3.3 kPa indicating a very weak structure. A similar technique used for bonding PU to glass resulted in a slightly higher bonding strength of 150 ± 10.1 kPa. The dip coating method gave a bond strength of 229.9 ± 24.3 kPa, substantially higher than the oxygen plasma method. Dip coating transfers some of the THF to the PU surface, dissolves it and when brought in close contact with the other PU film during bonding, partially dissolves the other surface. After curing, material from both substrates fuses and a tight bond is formed. Similarly, using a more precise micro-contact printing method where the amount of THF loaded onto the PU substrate is controlled and uniform yielded an even higher bond strength of 326.4 ± 19.6 kPa.

The various bonding methods were also characterized in terms of changes induced in the channel shape. The width and height of the microchannels in the PU replicas were measured using SEM images. The PU replicas retained the width of the SU-8 mould for both the wet and dry bonding methods. However, there were significant differences in the channel heights between the two methods. As expected, the channel height in the dry bonding method was the same as in the SU-8 mould. However, for the wet bonded channels the heights were lower than the height of the SU-8 mould. This indicates that the dissolution of the bonding surfaces and the subsequent application of a force during the bonding process leads to relocation of material and reduction in the channel height. This effect can be minimized by reducing the amount of THF used in the dip coating and micro-contact printing processes. These results suggest that the dry bonding method is better suited for channels of small cross section.

Electroosmotic mobility and dielectric performance

Other characteristics, that may be of importance in microfluidic Electroosmotic flow (EOF) was measured by tracking the movement of 1 μm neutral polystyrene particles in buffer solution at pH varying from 4 to 10 and voltage from 100 V to 200 V applied across 1 cm long microchannels. The particle motion was recorded and analyzed by microparticle image velocimetry (TSI) to obtain the electroosmotic velocity. The electroosmotic mobility (velocity divided by applied electric field) was found to be 2.47 × 10^{-8} m^2 V^{-1} s^{-1} at pH 7, slightly smaller than reported for PDMS (3.8 × 10^{-8} m^2 V^{-1} s^{-1}).[88] Both PU and PDMS[89] showed increasing electroosmotic mobility with increasing pH.

Protein adsorption

Biofouling is a significant issue in many applications and in blood contacting devices it is particularly problematic because of its propensity to initiate the blood coagulation cascade. Once coagulation is triggered, a fibrin clot will soon form and for microfluidic devices that have limited space, blockages would be detrimental to their continued function. This effect was tested by filling native PDMS microfluidic channels (L 3 cm × W 1 mm × H 100 μm) with human blood and observing clot formation. Within five min of incubation at room temperature, a clot formed and immediately stopped the flow through the device (data not shown).

For these experiments thin films as well as microchannels made from PDMS, unmodified PU and PEO-modified PU were used. Adsorption was found to be similar on unmodified PDMS and PU for both films and devices (Fig. 10). The PEO-modified PU device samples showed a significant reduction in adsorption >80% compared to unmodified PDMS and PU. The similar levels of fibrinogen adsorption observed on devices and films

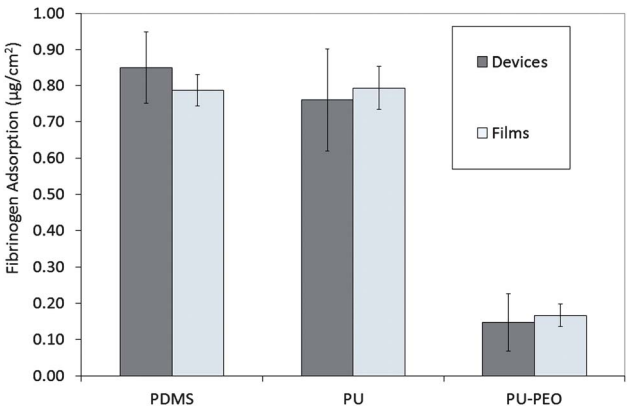


Fig. 10 Fibrinogen adsorption (1 mg mL^{-1} in PBS, 3 h) to devices and films. Data are means ± SD, n = 3.

Table 2 Burst pressures of sealed PU microchannels. Data are means ± SD, n = 5

	PU/PU O_2 plasma	PU/Glass O_2 plasma	PU/PU dip-coating	PU/PU μcontact printing	PDMS/PDMS O_2 plasma
Pressure (kPa)	42.2 ± 3.3	150.4 ± 10.1	229.9 ± 24.3	326.4 ± 19.6	300
Failure	Delamination	Delamination	Burst at edge	Leakage at connector	Burst at edge

confirmed that the surface modification process as adapted for the microfluidic devices was successful. It is worth mentioning that although the toluene used for PEO modification causes swelling (ratio 1.07) of PU, it barely affects the surface modification inside devices as our results show. These low levels of fibrinogen adsorption are expected to translate to reduced platelet adhesion and reduced procoagulant activity. Further investigation of these and other biological responses are warranted.

Conclusion

A new fabrication method for PU-based microfluidic devices was developed. Devices fabricated using biomedical grade PU showed similar properties to PDMS such as replica quality (roughness of 11 nm), bonding strength (326.4 kPa), optical transparency (96% that of glass) and solvent compatibility (better than PDMS). The PU surfaces showed increased hydrophilicity compared to PDMS and were amenable to chemical modification. Three bonding methods were developed that could cater to various application specific factors such as convenience (dip coating), high bonding strength (micro-contact printing) and nanostructural features (oxygen plasma treatment). Micro-contact printing provides the best performance for most microfluidic applications that have channel size in the micrometre scale. An integrated fabrication of interconnects facilitates the tubing processes for flow connection in microfluidic devices and the entire device has the ability to withstand a pressure up to 326.4 kPa. An *in situ* surface modification method successfully demonstrated the grafting of PEO to PU inside moulded and sealed microfluidic devices. The reduced levels of fibrinogen adsorption (80%) observed on PEO modified PU devices in comparison to native PDMS and native PU, demonstrate successful modification of the inner device surfaces and provide a more biocompatible surface with potential for resistance to blood clot formation. Extending the micro-contact printing technique to smaller dimension channels and testing of clotting behaviour in surface modified PU channels are possible future avenues for research.

Acknowledgements

The authors wish to acknowledge support from Natural Science and Engineering Research Council of Canada (NSERC), Canada Research Chairs Program and the Ontario Ministry of Research and Innovation through their Early Researchers Award (ERA) Program.

Notes and references

1 T. A. Horbett and P. K. Weathersby, Adsorption of proteins from plasma to a series of hydrophilic-hydrophobic copolymers. I. Analysis with the *in situ* radioiodination technique, *J. Biomed. Mater. Res.*, 1981, **15**, 403–423.
2 C. F. Wertz and M. M. Santore, Fibrinogen Adsorption on Hydrophilic and Hydrophobic Surfaces: Geometrical and Energetic Aspects of Interfacial Relaxations, *Langmuir*, 2001, **18**, 706–715.
3 S. Tunc, *et al. In situ* conformational analysis of fibrinogen adsorbed on Si surfaces, *Colloids Surf., B*, 2005, **42**, 219–25.
4 X. Ren, M. Bachman, C. Sims, G. P. Li and N. Allbritton, Electroosmotic properties of microfluidic channels composed of poly(dimethylsiloxane), *J. Chromatogr., Biomed. Appl.*, 2001, **762**, 117–125.
5 S. L. Peterson, A. McDonald, P. L. Gourley and D. Y. Sasaki, Poly(dimethylsiloxane) thin films as biocompatible coatings for microfluidic devices: Cell culture and flow studies with glial cells, *J. Biomed. Mater. Res.*, 2005, **72A**, 10–18.
6 H. M. L. Tan, H. Fukuda, T. Akagi and T. Ichiki, Surface modification of poly(dimethylsiloxane) for controlling biological cells' adhesion using a scanning radical microjet, *Thin Solid Films*, 2007, **515**, 5172–5178.
7 J. A. Vickers, M. M. Caulum and C. S. Henry, Generation of Hydrophilic Poly(dimethylsiloxane) for High-Performance Microchip Electrophoresis, *Anal. Chem.*, 2006, **78**, 7446–7452.
8 Y. Berdichevsky, J. Khandurina, A. Guttman and Y.-H. Lo, UV/ozone modification of poly(dimethylsiloxane) microfluidic channels, *Sens. Actuators, B*, 2004, **97**, 402–408.
9 K. Efimenko, W. E. Wallace and J. Genzer, Surface Modification of Sylgard-184 Poly(dimethyl siloxane) Networks by Ultraviolet and Ultraviolet/Ozone Treatment, *J. Colloid Interface Sci.*, 2002, **254**, 306–315.
10 H. Hillborg, N. Tomczak, A. Olàh, H. Schönherr and G. J. Vancso, Nanoscale Hydrophobic Recovery: A Chemical Force Microscopy Study of UV/Ozone-Treated Cross-Linked Poly(dimethylsiloxane), *Langmuir*, 2003, **20**, 785–794.
11 H.-Y. Chen and J. Lahann, Fabrication of Discontinuous Surface Patterns within Microfluidic Channels Using Photodefinable Vapor-Based Polymer Coatings, *Anal. Chem.*, 2005, **77**, 6909–6914.
12 H.-Y. Chen, Y. Elkasabi and J. Lahann, Surface Modification of Confined Microgeometries *via* Vapor-Deposited Polymer Coatings, *J. Am. Chem. Soc.*, 2005, **128**, 374–380.
13 H.-Y. Chen, A. A. McClelland, Z. Chen and J. Lahann, Solventless Adhesive Bonding Using Reactive Polymer Coatings, *Anal. Chem.*, 2008, **80**, 4119–4124.
14 M. Morra, On the aging of oxygen plasma-treated polydimethylsiloxane surfaces, *J. Colloid Interface Sci.*, 1990, **137**, 11–24.
15 H. Hillborg and U. W. Gedde, Hydrophobicity changes in silicone rubbers, *IEEE Trans. Dielectr. Electr. Insul.*, 1999, **6**, 703–717.
16 J. N. Lee, C. Park and G. M. Whitesides, Solvent Compatibility of Poly(dimethylsiloxane)-Based Microfluidic Devices, *Anal. Chem.*, 2003, **75**, 6544–6554.
17 S. Hu, *et al.* Surface Modification of Poly(dimethylsiloxane) Microfluidic Devices by Ultraviolet Polymer Grafting, *Anal. Chem.*, 2002, **74**, 4117–4123.
18 S. Lee and J. Vörös, An aqueous-based surface modification of poly(dimethylsiloxane) with poly(ethylene glycol) to prevent biofouling, *Langmuir: the ACS journal of surfaces and colloids*, 2005, **21**, 11957–62.
19 D. Wu, B. Zhao, Z. Dai, J. Qin and B. Lin, Grafting epoxy-modified hydrophilic polymers onto poly(dimethylsiloxane) microfluidic chip to resist nonspecific protein adsorption, *Lab Chip*, 2006, **6**, 942–7.
20 P.-Y. Yeh, N. a. a. Rossi, J. N. Kizhakkedathu and M. Chiao, A silicone-based microfluidic chip grafted with carboxyl functionalized hyperbranched polyglycerols for selective protein capture, *Microfluid. Nanofluid.*, 2009, **9**, 199–209.
21 D. J. Lyman, *et al.* The development and implantation of a polyurethane hemispherical artificial heart, *Transactions - American Society for Artificial Internal Organs*, 1971, **17**, 456–63.
22 J. W. Boretos and W. S. Pierce, Segmented polyurethane: a polyether polymer. An initial evaluation for biomedical applications, *J. Biomed. Mater. Res.*, 1968, **2**, 121–30.
23 J. L. Brash, B. K. Fritzinger and S. D. Bruck, Development of block copolyether-urethane intra-aortic balloons and other medical devices, *J. Biomed. Mater. Res.*, 1973, **7**, 313–34.
24 T. Devanathan, J. E. Sluetz and K. A. Young, *In vivo* thrombogenicity of implantable cardiac pacing leads, *Biomaterials, medical devices, and artificial organs*, 1980, **8**, 369–79.
25 T. Tsutsui, E. Imamura and H. Kayanagi, The development of nonstended trileaflet valve prosthesis. Artif Organs, *Artif Organs (Japan)*, 1981, **10**, 590–593.
26 D. Lyman, W. Seare and D. Albo, Polyurethane elastomers in surgery, *Int. J. Polym. Mater.*, 1977, **5**, 211–229.

27 A. Takahara, J. I. Tashita and T. Kajiyama, Microphase separated structure, surface composition and blood compatibility of segmented poly(urethaneureas) with various soft segment components, *Polymer*, 1985, **26**, 987–996.

28 A. F. Watkinson, J. Ellul, K. Entwisle, R. C. Mason and A. Adam, Esophageal carcinoma: initial results of palliative treatment with covered self-expanding endoprostheses, *Radiology*, 1995, **195**, 821–7.

29 P. Bruin, E. A. Meeuwsen, M. V. van Andel, J. G. Worst and A. J. Pennings, Autoclavable highly cross-linked polyurethane networks in ophthalmology, *Biomaterials*, 1993, **14**, 1089–97.

30 D. Bakker, *et al.* Biocompatibility of a polyether urethane, polypropylene oxide, and a polyether polyester copolymer. A qualitative and quantitative study of three alloplastic tympanic membrane materials in the rat middle ear, *J. Biomed. Mater. Res.*, 1990, **24**, 489–515.

31 D. K. Han *et al. In vivo* canine studies of a Sinkhole valve and vascular graft coated with biocompatible PU-PEO-SO3. *ASAIO journal (American Society for Artificial Internal Organs: 1992)* **39**, pp. M537–41.

32 W. J. van der Giessen, *et al.* Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries, *Circulation*, 1996, **94**, 1690–7.

33 N. Akiyama, K. Esato, K. Fujioka and N. Zempo, A comparison of CORVITA and expanded polytetrafluoroethylene vascular grafts implanted in the abdominal aortas of dogs, *Surg. Today*, 1997, **27**, 840–5.

34 T. Okoshi, G. Soldani, M. Goddard & P. M. Galletti. Penetrating micropores increase patency and achieve extensive endothelialization in small diameter polymer skin coated vascular grafts. *ASAIO journal (American Society for Artificial Internal Organs: 1992)* **42**, pp. M398–401.

35 Y. Marois, *et al.* Vascugraft microporous polyesterurethane arterial prosthesis as a thoraco-abdominal bypass in dogs, *Biomaterials*, 1996, **17**, 1289–300.

36 Y. Marois *et al.* A novel microporous polyurethane vascular graft: in vivo evaluation of the UTA prosthesis implanted as infra-renal aortic substitute in dogs. *Journal of investigative surgery: the official journal of the Academy of Surgical Research* **6**, pp. 273–88.

37 Y. Marois, *et al. In vivo* evaluation of hydrophobic and fibrillar microporous polyetherurethane urea graft, *Biomaterials*, 1989, **10**, 521–31.

38 J. L. Brash, Exploiting the current paradigm of blood-material interactions for the rational design of blood-compatible materials, *J. Biomater. Sci., Polym. Ed.*, 2000, **11**, 1135–1146.

39 J. Lee, H. Lee and J. Andrade, Blood compatibility of polyethylene oxide surfaces, *Prog. Polym. Sci.*, 1995, **20**, 1043–1079.

40 W. Feng, J. L. Brash and S. Zhu, Non-biofouling materials prepared by atom transfer radical polymerization grafting of 2-methacryloloxyethyl phosphorylcholine: separate effects of graft density and chain length on protein repulsion, *Biomaterials*, 2006, **27**, 847–55.

41 S. Martwiset, A. E. Koh and W. Chen, Nonfouling characteristics of dextran-containing surfaces, *Langmuir: the ACS journal of surfaces and colloids*, 2006, **22**, 8192–6.

42 N. Saito, C. Nojiri, S. Kuroda and K. Sakai, Photochemical grafting of alpha-propylsulphate-poly(ethylene oxide) on polyurethane surfaces and enhanced antithrombogenic potential, *Biomaterials*, 1997, **18**, 1195–7.

43 A. P. van der Heiden, D. Goebbels, A. P. Pijpers and L. H. Koole, A photochemical method for the surface modification of poly(etherurethanes) with phosphorylcholine-containing compounds to improve hemocompatibility, *J. Biomed. Mater. Res.*, 1997, **37**, 282–90.

44 K. Fujimoto, H. Inoue and Y. Ikada, Protein adsorption and platelet adhesion onto polyurethane grafted with methoxy-poly(ethylene glycol) methacrylate by plasma technique, *J. Biomed. Mater. Res.*, 1993, **27**, 1559–67.

45 K. Fujimoto, H. Tadokoro, Y. Ueda and Y. Ikada, Polyurethane surface modification by graft polymerization of acrylamide for reduced protein adsorption and platelet adhesion, *Biomaterials*, 1993, **14**, 442–8.

46 Y. H. Kim, D. K. Han, K. D. Park and S. H. Kim, Enhanced blood compatibility of polymers grafted by sulfonated PEO *via* a negative cilia concept, *Biomaterials*, 2003, **24**, 2213–2223.

47 C. Nojiri, *et al.* Blood compatibility of PEO grafted polyurethane and HEMA/styrene block copolymer surfaces, *J. Biomed. Mater. Res.*, 1990, **24**, 1151–71.

48 J. Tan and J. L. Brash, Nonfouling biomaterials based on polyethylene oxide-containing amphiphilic triblock copolymers as surface modifying additives: Synthesis and characterization of copolymers and surface properties of copolymer–polyurethane blends, *J. Appl. Polym. Sci.*, 2008, **108**, 1617–1628.

49 C. Freij-Larsson, T. Nylander, P. Jannasch and B. Wesslén, Adsorption behaviour of amphiphilic polymers at hydrophobic surfaces: effects on protein adsorption, *Biomaterials*, 1996, **17**, 2199–2207.

50 M. Amiji and K. Park, Prevention of protein adsorption and platelet adhesion on surfaces by PEO/PPO/PEO triblock copolymers, *Biomaterials*, 1992, **13**, 682–692.

51 J. H. Lee, J. Kopecek and J. D. Andrade, Protein-resistant surfaces prepared by PEO-containing block copolymer surfactants, *J. Biomed. Mater. Res.*, 1989, **23**, 351–68.

52 A. Folch, S. Mezzour and M. Du, Stacks of Microfabricated Structures as Scaffolds for Cell Culture and Tissue Engineering, *Tissue Engineering*, 2000, 207–214.

53 J. S. Kuo, *et al.* Microfabricating high-aspect-ratio structures in polyurethane-methacrylate (PUMA) disposable microfluidic devices, *Lab Chip*, 2009, **9**, 1951–6.

54 J.-Y. Shen, M. B.-E. Chan-Park, Z.-Q. Feng, V. Chan and Z.-W. Feng, UV-embossed microchannel in biocompatible polymeric film: application to control of cell shape and orientation of muscle cells, *J. Biomed. Mater. Res., Part B*, 2006, **77**, 423–30.

55 J. Xu, L. Locascio, M. Gaitan and C. S. Lee, Room-Temperature Imprinting Method for Plastic Microchannel Fabrication, *Anal. Chem.*, 2000, **72**, 1930–1933.

56 J. S. Rossier, *et al.* Plasma etched polymer microelectrochemical systems, *Lab Chip*, 2002, **2**, 145–50.

57 K. T. Haraldsson, *et al.* 3D polymeric microfluidic device fabrication *via* contact liquid photolithographic polymerization (CLiPP), *Sens. Actuators, B*, 2006, **113**, 454–460.

58 E. Piccin, *et al.* Polyurethane from biosource as a new material for fabrication of microfluidic devices by rapid prototyping, *J. Chromatogr., A*, 2007, **1173**, 151–8.

59 T. Thorsen, R. W. Roberts, F. H. Arnold and S. R. Quake, Dynamic Pattern Formation in a Vesicle-Generating Microfluidic Device, *Phys. Rev. Lett.*, 2001, **86**, 4163–4166.

60 Y. S. Kim, H. H. Lee and P. T. Hammond, High density nanostructure transfer in soft molding using polyurethane acrylate molds and polyelectrolyte multilayers, *Nanotechnology*, 2003, **14**, 1140–1144.

61 K. N. Sask, L. R. Berry, A. K. C. Chan and J. L. Brash, Modification of Polyurethane Surface with an Antithrombin-Heparin Complex for Blood Contact: Influence of Molecular Weight of Polyethylene Oxide Used as a Linker/Spacer, *Langmuir*, 2011, DOI: 10.1021/la203821g.

62 M. Böswald, *et al.* Biocompatibility testing of a new silver-impregnated catheter *in vivo*, *Infection*, 1999, **27**, S38–S42.

63 M. Böswald, *et al.* Thrombogenicity testing of central venous catheters *in vitro*, *Infection*, 1999, **27**, S30–S33.

64 T. Hentschel and H. Münstedt, Thermoplastic polyurethane—The material used for the erlanger silver catheter, *Infection*, 1999, **27**, S43–S45.

65 M.-C. Belanger, *et al.* Selection of a Polyurethane Membrane for the Manufacture of Ventricles for a Totally Implantable Artificial Heart: Blood Compatibility and Biocompatibility Studies, *Artif. Organs*, 2000, **24**, 879–888.

66 R. M. Cornelius, J. Macri and J. L. Brash, *Journal of biomedical materials research Part A*, 2011, 109–115.

67 V. Barron, Durability of APC2/Polyurethane adhesive joints for biomedical applications, *Int. J. Adhes. Adhes.*, 2000, **20**, 361–366.

68 C. Moraes, *et al.* Integrating polyurethane culture substrates into poly(dimethylsiloxane) microdevices, *Biomaterials*, 2009, **30**, 5241–50.

69 A. V. Pattekar and M. V. Kothare, Novel microfluidic interconnectors for high temperature and pressure applications, *J. Micromech. Microeng.*, 2003, **13**, 337–345.

70 E. S. Lee, D. Howard, E. Liang, S. D. Collins and R. L. Smith, Removable tubing interconnects for glass-based micro-fluidic systems made using ECDM, *J. Micromech. Microeng.*, 2004, **14**, 535–541.

71 T.-J. Yao, S. Lee, W. Fang and Y.-C. Tai, in *Micro Electro Mechanical Systems, 2000. MEMS 2000. The Thirteenth Annual International Conference on*, 2000, pp. 624–627.
72 A. A. S. Bhagat, P. Jothimuthu, A. Pais and I. Papautsky, Re-usable quick-release interconnect for characterization of microfluidic systems, *J. Micromech. Microeng.*, 2007, **17**, 42–49.
73 J.-H. Tsai and L. Lin, Micro-to-macro fluidic interconnectors with an integrated polymer sealant, *J. Micromech. Microeng.*, 2001, **11**, 577–581.
74 A. Puntambekar and C. H. Ahn, Self-aligning microfluidic interconnects for glass- and plastic-based microfluidic systems, *J. Micromech. Microeng.*, 2002, **12**, 35–40.
75 J. Liu, C. Hansen and S. R. Quake, Solving the "World-to-Chip" Interface Problem with a Microfluidic Matrix, *Anal. Chem.*, 2003, **75**, 4718–4723.
76 D. a. Chang-Yen, D. G. Myszka and B. K. Gale, A Novel PDMS Microfluidic Spotter for Fabrication of Protein Chips and Microarrays, *J. Microelectromech. Syst.*, 2006, **15**, 1145–1151.
77 R. Lo and E. Meng, Reusable, adhesiveless and arrayed in-plane microfluidic interconnects, *J. Micromech. Microeng.*, 2011, **21**, 054021.
78 I. K. Glasgow, D. J. Beebe and V. E. White, Design rules for polyimide solvent bonding, *Sensors and Materials*, 1999, **11**, 269–278.
79 C. Lin, C. Chao and C. Lan, Low azeotropic solvent for bonding of PMMA microfluidic devices, *Sens. Actuators, B*, 2007, **121**, 698–705.
80 F.-C. Huang, Y.-F. Chen and G.-B. Lee, CE chips fabricated by injection molding and polyethylene/thermoplastic elastomer film packaging methods, *Electrophoresis*, 2007, **28**, 1130–7.
81 M. A. Roberts, J. S. Rossier, P. Bercier and H. Girault, UV Laser Machined Polymer Substrates for the Development of Microdiagnostic Systems, *Anal. Chem.*, 1997, **69**, 2035–42.
82 H. Klank, J. P. Kutter and O. Geschke, CO(2)-laser micromachining and back-end processing for rapid production of PMMA-based microfluidic systems, *Lab Chip*, 2002, **2**, 242–6.
83 H. Kim, S. Member & K. Najafi. *Characterization of Low-Temperature Wafer Bonding Using Thin-Film Parylene*. **14**, 1347–1355 (2005).
84 P. Rezai, P. R. Selvaganapathy and G. R. Wohl, Plasma enhanced bonding of polydimethylsiloxane with parylene and its optimization, *J. Micromech. Microeng.*, 2011, **21**, 065024.
85 D.-G. Choi, S. G. Jang, H. K. Yu and S.-M. Yang, Two-Dimensional Polymer Nanopattern by Using Particle-Assisted Soft Lithography, *Chem. Mater.*, 2004, **16**, 3410–3413.
86 J. C. McDonald and G. M. Whitesides, Poly(dimethylsiloxane) as a Material for Fabricating Microfluidic Devices, *Acc. Chem. Res.*, 2002, **35**, 491–499.
87 D. Rosu, L. Rosu and C. N. Cascaval, IR-change and yellowing of polyurethane as a result of UV irradiation, *Polym. Degrad. Stab.*, 2009, **94**, 591–596.
88 Y. Liu, J. C. Fanguy, J. M. Bledsoe and C. S. Henry, Dynamic Coating Using Polyelectrolyte Multilayers for Chemical Control of Electroosmotic Flow in Capillary Electrophoresis Microchips, *Anal. Chem.*, 2000, **72**, 5939–5944.
89 V. Tandon, S. K. Bhagavatula, W. C. Nelson and B. J. Kirby, Zeta potential and electroosmotic mobility in microfluidic devices fabricated from hydrophobic polymers: 1. The origins of charge, *Electrophoresis*, 2008, **29**, 1092–101.

