Chapter 4

Solvent-Resistant Fluorinated-Norbornene (FNB) Microfluidic Devices

4.1 Introduction

In pursuit of the goal of fabricating solvent-resistant microfluidic devices from permeable elastic materials we first tapped into the vast range of polymers that are commercially available. Since these materials were not designed with microfluidics applications in mind, we found most solvent resistant materials to be lacking in terms of mechanical properties, such as elasticity, or in terms of processability for our purposes (see Chapter 3). Collaborations with polymer chemists to develop new materials turned out to be far more fruitful, as the interactive development process led to the invention of novel materials ideally suited to the fabrication of elastomeric solvent-resistant microfluidic devices.

In this chapter, I discuss the results of one such collaboration with chemists at Materia Incorporated (Pasadena, CA), which culminated in the successful fabrication of microfluidic devices containing functional push-down microvalves. The first section gives a brief overview of the material chemistry, followed by two sections giving accounts of important results and research directions for two initial "generations" of devices. First-generation devices were composed of non-solvent-resistant norbornene-based elastomers with a CYTOP coating to provide protection from solvents, while second-generation devices incorporated a solvent-resistant norbornene-based elastomer in their bottom layer and did not require this coating. Unfortunately, our supply of material was exhausted soon after successful demonstration of valves in these devices and work did not proceed further for some time. However, due to collaborations with new partners, results relating to a third generation of devices—composed entirely of solvent-resistant elastomer—have recently emerged. I briefly highlight these results and discuss prospects for Materia's fluorinated polymers in the last section.

4.2 Chemistry

Materia specializes in the development of polymers and catalysts based on ring opening metathesis polymerization (ROMP), a chemistry that became practical with the development of catalysts by Grubbs *et al.* [95]. The mechanism of this chemistry is shown in Figure 4.1. We worked primarily with polymers based on monomers derived from norbornene (NB) and dicyclopentadiene (DCPD).

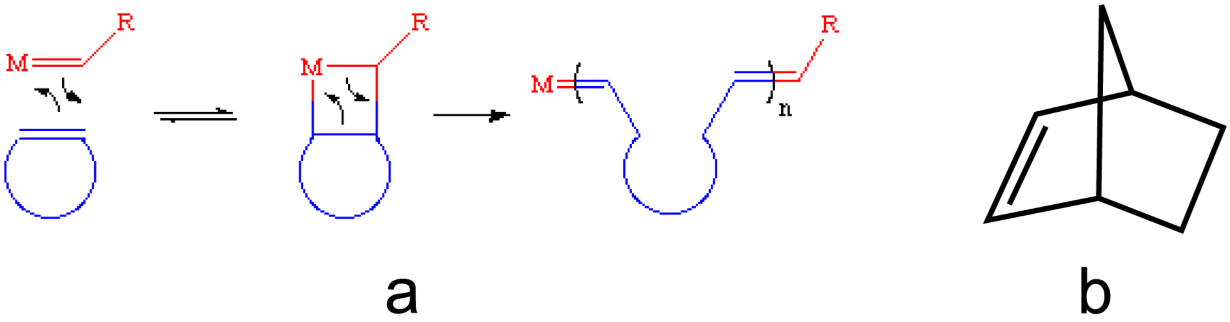

Figure 4.1: **Ring-opening metathesis polymerization (ROMP)**. (a) Reaction mechanism. A strained ring structure (bottom structure in first stage) is opened by a metal alkylidene catalyst (top structure), driven by relief of ring strain. At the end of the reaction (third stage), the catalyst remains bound to the opened ring and is available for further reactions. Considering the strained ring as a monomer, one can see a polymer grows by the insertion of ring-opened monomers between the catalyst and the rest of the structure. (Reproduced from Rob Toreki's Organometallic HyperTextBook, `http://www.ilpi.com/organomet/romp.html`. Copyright Rob Toreki, 2005.) (b) The structure of norbornene, from which one class of monomers can be derived. Materia's solvent-resist polymers evaluated in this work are built from monomers that are norbornene derivatives.

Polymerization produces monodisperse chains that are intertwined into an amorphous uncrosslinked elastomeric material. These materials are living catalyst systems, which turns out to be convenient for bonding because polymerization can continue into the adjacent layer when two partially cured polymers are brought into contact. Solvent resistance is determined primarily by the particular monomer used, while mechanical properties are also affected by degree of cross-linking (if branched monomers are incorporated) as well as the rate of polymerization. Typically, polymers are prepared from a mixture of one or more monomers, a catalyst, a solvent to dissolve the catalyst, and additives such as inhibitors, antioxidants, and adhesion promoters. Polymerization is an exothermic process, proceeding first through a gel phase then to a solid material. One controls the rate and maximum temperature of the reaction by formulation as well as by controlling the ambient temperature, initial reagent temperature, and the total mass of material. If polymerization is too fast, a phenomenon called "worming" is observed, wherein high speed gas bubbles are generated that leave hollow paths in the cured polymer. A high exotherm temperature may also have the detrimental effect of damaging the catalyst and preventing bonding in later fabrication steps.

4.3 First-generation devices: CYTOP coating

Initially, Materia supplied us with materials polymerized from proprietary formulations of hexylnorbornene (HNB), decylnorbornene (DNB), ethylidene norbornene (ENB), and some dicyclopentadiene (DCPD) derivatives. Early evaluation indicated that these polymers were susceptible to attack by many solvents including dichloromethane, acetonitrile, and tetrahydrofuran—solvents that interested us due to their role in DNA synthesis chemistry (see Chapter 7). The polymers exhibited considerable swelling and discoloration immediately upon exposure to solvents, and in many cases, exposed areas were permanently damaged by pitting or conversion to a sticky residue. Some of the materials did however possess qualitatively good elastic modulus, though complete recovery from the deformed state was often slow—up to several seconds. The elastomers were robust and could withstand considerable elongation (up to 100–200%); samples could even be folded back on themselves without cracking or breaking as we have observed in many other materials.

Solvent-resistant fluoromonomers were not yet available in the early stages of this work, so we attempted to confer resistance by coating with CYTOP 809A (Sigma Aldrich), a fluoropolymer coating material we had tried in conjunction with PDMS (see Chapter 3). For simplicity, we fabricated devices with a push-down valve architecture; since all fluid channels are located in the bottom layer in such devices, a protective CYTOP coating is only needed on the bottom surface (see Chapter 2). Push-up valves expose both layers to solvents in fluid channels and would require applying the coating inside channels or applying coatings to two layers—on the bottom of the top (fluid) layer and on the top of the bottom (control) layer—and fusing them together. Both approaches have proven problematic in past experience with other materials.

The next section describes our efforts to develop an effective protocol for coating polymer samples with CYTOP. Subsequent sections describe in detail the steps involved in actual microfluidic device fabrication: preparation of the coated thin layer and the uncoated thick layer, bonding of the layers, and connection of devices to the outside world. While in principle very similar to PDMS device fabrication, the details are very different due to particular properties of the polymers involved.

4.3.1 Development of CYTOP coating procedure

Initially, we tried spin-coating the CYTOP directly onto 1-layer fluidic devices. Polymer samples with a variety of proprietary formulations were molded on silicon wafers containing a dense pattern of microchannel features. To apply the coating, each polymer sample was mounted directly on the spin-coater chuck with channels facing upwards and spun immediately after depositing a small volume of CYTOP on the surface. Fortunately, CYTOP had good wetting properties on all materials evaluated. Undiluted CYTOP is very viscous and resulted in very irregular, incomplete coatings. Instead, we diluted CYTOP 1:3 in Fluorinert FC-75 (3M Corporation, St. Paul, MN) for spinning. Typically, we pipetted 400 μL of this mixture for each device and spun at 500 RPM for 10 seconds followed by 3000 RPM for 20 seconds. It was critical to begin spinning immediately due to the high volatility of the solvent. Devices were then baked for 1 h at 80°C followed by 1 h at 170°C. The latter is an annealing step, required because the very low solids content (9% initially; 2.25% after dilution) of the CYTOP mixture otherwise leads to high shrinkage and stress, potentially resulting in incomplete coatings. Initially having a starburst appearance with about 1 μm in thickness variation (determined by profilometry), the coating becomes uniform and smooth after this step.

The high temperature baking caused severe discolouration and rigidification in early DCPD materials due to oxidation. To mitigate this effect, antioxidants were included in subsequent formulations. In addition, Materia fabricated a gas-tight aluminum chamber that could be placed in the oven. Prior to baking, we placed the sample in this chamber and evacuated it for 5–10 min to remove the air (and oxygen). We also tried purging with helium gas but observed a large number of bubbles in samples after baking. Internal measurements with a thermocouple indicated that the chamber takes 75 min to heat up from 80°C to 170°C; therefore the duration of the annealing step was increased to 2 h.

The resulting coatings were observed to be well adhered to the underlying polymer in all samples. Coatings were evaluated for solvent resistance by placing droplets of solvents on the surface and then looking for qualitative effects such as swelling and distortion, discolouration, and residue. Several CYTOP-coated polymers exhibited excellent resistance to dichloromethane, acetonitrile, and tetrahydrofuran in flat regions; however, areas with microchannels were susceptible to attack in all samples. Profiling the surface immediately after dichloromethane exposure revealed significant swelling within 10–20 μm of microchannel walls with less swelling further away (Figure 4.2). We hypothesized that the channel side-walls were not being completely coated, perhaps due to the CYTOP flowing off of walls and pooling in the lower features (microchannels) during coating or annealing. In one sample, we profiled a step edge of the CYTOP coating and determined its thickness to be 3–4 μm. The profile of the channels in this sample, shown in Figure 4.2, indicates a channel depth of about 44 μm. This result is consistent with CYTOP pooling as the height of channel features on the silicon mold from which the polymer was cast was 46 μm, indicating a 2 μm loss. On samples with thicker coatings, a greater depth discrepancy was observed.

Testing coated polymers is a tedious process, requiring exposure to several different solvents (as some polymers exhibited resistance to certain solvents even when uncoated) and observation at many exposed locations often over long periods of time. We developed a rapid method for evaluating coating integrity by exposure to droplets of 96% sulphuric acid. Upon contact with any of the polymer samples, the acid causes nearly immediate charring of unprotected areas. Annealed

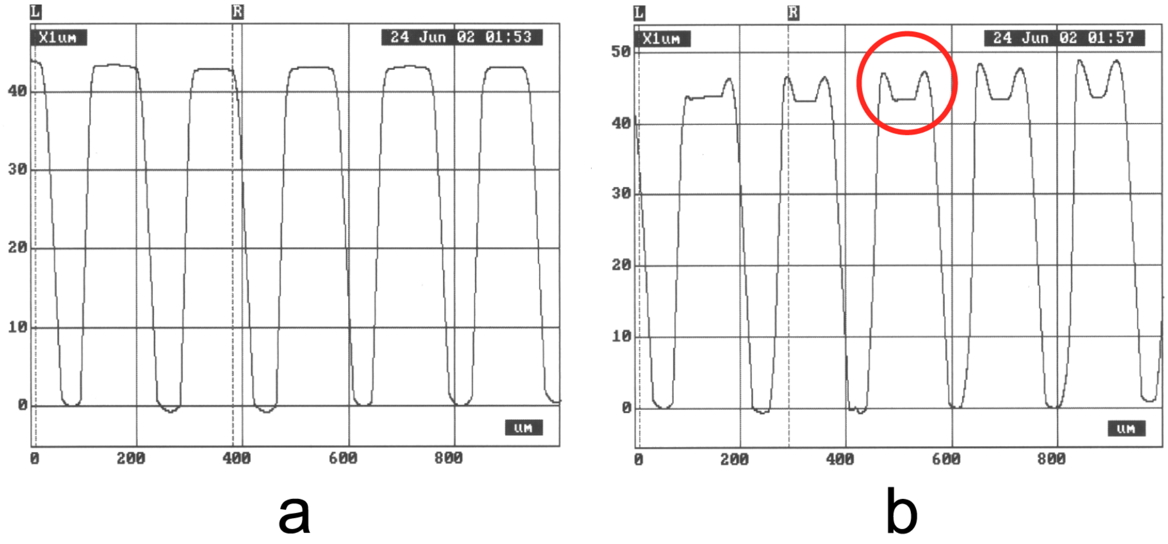

Figure 4.2: **Effect of dichloromethane exposure on surface profile of CYTOP-coated device**. Surface profile over several 100 μm-wide microchannels of a CYTOP-coated Materia device (a) before and (b) after exposure to droplets of dichloromethane. No swelling was observed in regions away from microchannels; however, swelling was visible by eye in regions with channel features. The profile shows that the highest swelling is at the edges of microchannels, suggesting that the side walls are not adequately coated. The height of channel features on the original mold was 46 μm; thus the 44 μm height in these profiles suggests that the CYTOP coating procedure results in the loss of 2 μm in feature height, perhaps due to the CYTOP pooling at the bottom of channels. This particular coated device was made from proprietary formulation B-47-012-B.

CYTOP provides a complete barrier that in one experiment protected a sample for more than a year, exhibiting no visible damage other than a small change in wetting properties of the exposed CYTOP. Samples were tested by moving a large droplet around the surface. Pinholes or other defects in the CYTOP coating where the acid can seep through lead to charring, sometimes preceeded by a discolouration to red, brown, then black. The high contrast and rapidity of the colour change made this test particularly convenient. With this testing method, CYTOP layers applied by spin coating were confirmed to have discontinuities in the vicinity of the microchannel patterns on the surface.

A dip-coating procedure was evaluated next. Devices were dipped face down in a 1:30 CYTOP dilution and allowed to dry at 80°C. Multiple coatings were applied, with the sample in a different orientation during each drying step. It was hoped that vertical device orientations would allow channel side walls to be properly coated. However, after annealing, these samples did not exhibit improved resistance in regions of the surface containing microchannels. Flat regions were resistant, however, indicating that the much thinner CYTOP coating achieved by this method was a sufficient barrier.

Our best coatings were obtained by first coating the patterned wafer with CYTOP then transferring this coating to a polymer by polymerizing the resin directly on top of it. One significant advantage of this technique is that the coated device is an exact replica of the mold; with spin and dip coating, the added CYTOP affects critical device dimensions such as channel depth and width. To facilitate release of CYTOP from the mold, wafers were treated with a fluorosilane vapour (see Appendix A.1.5). Though the coating can be applied by many means, we found that spraying diluted CYTOP (1:30) with an airbrush resulted in superior coverage. Presumably due to the large surface to volume ratio resulting from atomization, droplets of CYTOP dry immediately or soon after impact, thus remaining in place on all parts of the mold surface, including channel walls. When spin or dip coated, the CYTOP remains in liquid form sufficiently long to flow off of walls and into valleys before drying. Wafers were thoroughly coated by spraying about 1.75 mL of CYTOP solution from a variety of directions and then dried by baking at 80°C. Profilometry indicated that the coatings had a thickness in the range 0.5–1.0 μm with a roughness of about 20–50 nm. Altough other polymers (e.g., PDMS) exhibit poor adhesion to CYTOP even when polymerized in place on top of the coating, several Materia polymers had sufficient adhesion that they lifted the CYTOP layer from the wafer. We evaluated dozens of formulations for this specific ability in addition to high elasticity, eventually settling upon the following recipe: 5g HNB, 150 mg Ethanox (antioxidant), 50 mg KR55 (adhesion promoter), 5 mg C848 (catalyst), 5 mg TPP (inhibitor), 0.5 mL toluene. Since the resins tend not to wet the CYTOP surface, coated wafers were treated for 3 min with oxygen plasma prior to spraying, pouring, or spinning the resin.

In 2-layer device fabrication, the thin fluid layer remains on the wafer while the control layer is bonded to it. This implies that annealing of the CYTOP layer would either have to be performed with the thin layer alone on the wafer or after assembly of a completed 2-layer device. The latter was not possible, as the HNB resin exhibited signs of melting and channel collapse at temperatures below 108°C, the glass transition temperature of CYTOP [47], which is the minimum temperature at which annealing is effective. Melting is not important when baking the thin layer by itself; however the CYTOP was found to become permanently bonded to the wafer or photoresist when baked in place. Fortunately, solvent and sulphuric acid exposure indicated that annealing was not necessary—the unannealed coating provided a sufficient barrier, presumably due to the thorough coverage achieved by spraying.

4.3.2 Fabricating the thin (fluid) layer

Details of the CYTOP-coating procedure were next adapted to produce the thin, coated fluid layer for 2-layer microfluidic devices. One of the most significant obstacles we encountered in device fabrication was polymerizing the thin (fluid) layers with a repeatable thickness. The difficulty stems partly from the extremely low viscosity of the Materia resins. The viscosity of the HNB resin is 12 cP, compared with Sylgard 184 PDMS prepolymer, which has a viscosity of 7000–8000 cP as measured by the same instrument. Repeatability is also hindered by the short time over which the viscosity changes once the catalyst is mixed into the resin. However, incorporation of inhibitor and cooling of the resin was sufficient to maintain the low viscosity for an extended period.

In our push-down devices, fluid channels were typically 100 μm wide and 10–15 μm deep. We strove for a total fluid layer thickness of 20–30 μm to achieve thin valve membranes that could be actuated at reasonably low pressures. The best coating method we found for our first-generation devices was spin coating immediately after mixing the resin with catalyst. Spin-coating parameters were 180–200 RPM, 10 s spin time, and 3 s ramp time. This extremely low speed is not sufficient to expel excess material from the wafer, so it was necessary to blot the edge with a Kimwipe *during* spinning to prevent this liquid from reflowing across the wafer when spinning was stopped. Wafers were baked at 45°C for several minutes immediately after coating to polymerize the layer. Coating thickness was often but not always in the target range of 20–30 μm. To avoid variations due to viscosity buildup, an individual 2 g batch of monomer was prepared for each wafer, prechilled to –20°C, and mixed with catalyst solution (containing all other ingredients) immediately prior to spinning.

We tried numerous other methods to achieve thin polymer layers including pouring and spraying but both resulted in very poorly controlled layer thicknesses, even with accurately measured resin volumes.

4.3.3 Fabricating the thick (control) layer

Control layers were fabricated by pouring catalyzed resin onto a control layer mold treated with fluorosilane. Molds were patterned with thick SU-8 photoresist so the resulting deep, square-profile channels could not easily collapse during the baking step required for layer-layer adhesion. To conserve material, a mold barrier or “dam” was placed around the patterned area. PDMS and urethane gaskets provided an inadequate seal for the low viscosity resin so aluminum barriers were fabricated. The dam was affixed to the mold with a small amount of catalyzed HNB resin. Aluminum foil wrapped around the bottom of the wafer and pressed into an appropriate shape is also sufficient as a barrier, though a small amount of material may leak under the foil, requiring device trimming (e.g., with scissors) prior to use. Wafers were placed on tinfoil directly on a hotplate set to approximately 40–50°C. Pre-cooled resin was catalyzed and poured into the barriers. Any visible air bubbles near channel features were dislodged by jets of resin squirted by a pipette. To ensure the cast device has a flat upper surface (instead of a curved meniscus), a 2×3 inch glass slide was placed over the filled mold and a weight placed on top. A small opening was left at one corner to allow the escape of air bubbles. One corner of the mold was gently warmed with a heat gun until a slow polymerization exotherm was initiated. Samples were then allowed to cool for several minutes before removal from the molds. This procedure is shown in Figure 4.3.

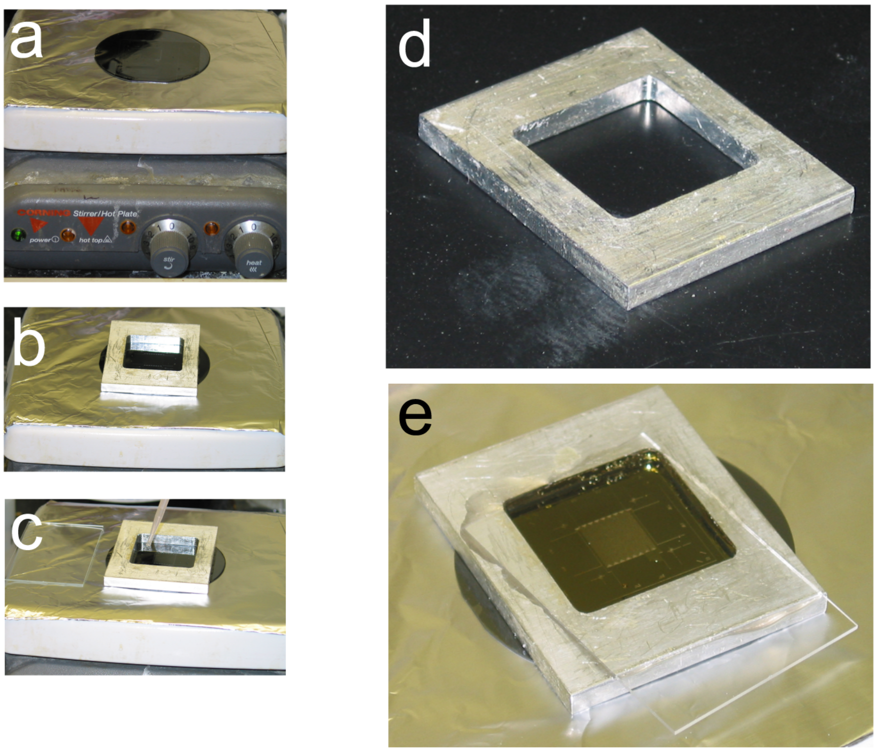

Figure 4.3: **Fabrication of thick device layers from Materia resin**. (a) A control layer mold (patterned 3-inch silicon wafer) is placed on a hot plate surface. (b) An aluminum barrier mold is affixed to the wafer by polymerizing HNB (as a glue). (c) The resin is pipetted onto the mold within the barrier, and a glass slide is placed on top. The resin then polymerizes. (d) A photograph of the aluminum barrier mold. (e) A device in a mold immediately after the polymerization exotherm. At this point, the glass slide would be removed, and the device would be cut out of the mold for hole punching and assembly with the fluid (thin) layer.

After many variations in formulation, the following formula for the thick layer was developed. 7 g HNB, 7 g ENB, 2.5 g DNB, and 500 mg Ethanox were heated to dissolve the antioxidant, filtered with a 0.2 μm syringe filter[1], and then chilled to –20°C. The resin was catalyzed with 10 mg C848

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[1] Filtering eliminates undissolved antioxidant and contaminants that build up in the ENB over time.

catalyst and 11 mg TPP inhibitor dissolved in about 0.5 mL toluene. This quantity of material was sufficient to fill two aluminum barriers. HNB provides overall flexibility and elasticity that helps the thick layer to seal to the thin layer, while the presence of ENB in the formulation provides rigidity that prevents channel collapse during the baking step to bond layers. DNB confers some flexibility that is useful during mold release.

Due to the toughness of the surface layer of this polymer formulation, holes could not be punched easily without bending the punch tool or Luer stubs that are normally used for PDMS devices. By freezing the polymer, we could create consistent holes by drilling but we observed significant contamination by dust and oil. The best method we found was to melt holes through the polymer. A Luer stub is heated with a Bunsen burner until red hot and then rapidly plunged through the thick polymer layer from the channel side at the desired point. The layer is then immersed in ice water for a few seconds with the Luer stub still in place. After cooling, the stub is removed, leaving a smooth hole. The Luer stub can be reheated to burn out the polymer core that is taken from the hole. Note that because the thick layer exhibits only moderate elasticity, the punch size was matched exactly to the tubing size that will be inserted. (In PDMS devices, the punched hole is typically somewhat smaller than the tubing size.) Though not a concern for our experiments, in a production setting, a technique such as laser drilling could conceivably be used to create these holes.

4.3.4 Bonding layers

Because Materia polymers are a living catalyst system, fresh monomer sprayed or poured on a cured device will polymerize onto the previous surface into a monolithic structure. One possible microfluidic-device-bonding strategy is thus to use a thin layer of resin as a glue between the fluid and control layers; however, we were not able to coat the material sufficiently thinly that it did not clog channels in the control layer. A strategy that did work well was placing the two solidified surfaces into contact at an elevated temperature for a prolonged period. Best results were obtained if the layers were bonded immediately after they solidified. (Layers could be frozen under dry conditions to prolong the processing window.) It is our hypothesis that barely cured polymers contain monomers or oligomers that can further react, thus forming polymer chains that extend between two layers to join them covalently. When fabricating the control layers, it is important that the exotherm be slow to avoid high temperatures that could destroy the catalyst thus preventing further chain elongation.

The thick layer was aligned to the thin layer (still affixed to the fluid layer mold) under a stereoscope. Care is required, as layers cannot be peeled apart in case of alignment error due to the high tackiness of these polymers. Since we were primarily interested in demonstrating valves, our devices consisted of an easily aligned design: a dense pattern of parallel fluid channels crossed by five widely spaced control channels in the perpendicular direction. As long as some channels intersected, alignment was successful. Once the layers were in contact, they were baked at 45°C for 2–3 hours. Higher temperatures or longer bake times led to collapsing of the control channel features. Likely this is due to the incomplete polymerization in the first stage—perhaps a higher exotherm temperature could help. While significant adhesion could be obtained by putting clean surfaces in contact, we also found that spraying surfaces with catalyst dissolved in toluene (no TPP or antioxidant) can improve bonding. Using an airbrush at a distance of 10–20 cm, we applied a few very brief (less than 1 second) sprays of catalyst mist—just enough to uniformly cover the surface. Both surfaces were sprayed then degassed for 5–10 min to ensure the toluene had completely evaporated; otherwise, bubbles form between layers during the baking step and interfere with adhesion. Several devices were capable of being pressurized to 22–25 psi for sustained periods without delamination. One drawback of using the catalyst spray is that particles remain between the surfaces in the final device. Occasionally these are located in channels and could lead to contamination. In addition, some are quite large (up to 8 μm) and could interfere with layer-layer bonding.

4.3.5 Testing microfluidic devices

For testing, bonded microfluidic devices were peeled from the fluid layer mold and affixed to glass slides. Since the CYTOP layer exhibits very poor adhesion to glass, I constructed a number of fluid delivery jigs to hold the device onto the glass. One is shown in Figures 4.4 and 4.5. In this setup, solvents are delivered to the fluid layer through holes drilled through the glass slide (see

Appendix A.2.3). This eliminates the need to punch input ports through the whole device, therefore avoiding damage to the CYTOP coating and preventing exposure of the upper, non-resistant part of the device to solvents. The jig simultaneously held O-rings in place on one side of the glass slide while holding the microfluidic device in place on the other. The bottom plate accepted HPLC fittings aligned with the O-rings to allow solvents to be delivered by microbore tubing under syringe or regulated nitrogen pressure. Four thumbscrews provided fine adjustments to control the force applied to the whole "sandwich". Note that the top surface of the microfluidc device must be very flat in order for the force to be applied evenly.

Though we demonstrated working valves and successfully delivered solvents at low pressures, this method was not very robust, and we nearly always observed delamination between the device and the glass slide. Presumably the problem stems from the poor adhesion of CYTOP to glass. Since the walls between channels are not adhered to the substrate, it is probably quite easy for pressurized fluid in a channel to slightly lift the channel upwards, creating a small locally delaminated area.

CYTOP-coated devices suffered from the additional problem that they could not easily be removed from the fluid layer mold. Removal frequently tore tiny pieces of CYTOP away from the thin layer (rendering these regions non-resistant) or resulted in severe stretching of the polymer that led to cracking of the coating. Making molds with different resists, different release coatings, or even out of different materials (such as DCPD and urethane) did not resolve this issue. Fortunately most of the lessons learned were transferable to the fabrication of second-generation devices when fluorinated monomers became available.

4.4 Second-generation devices: FNB fluid layer

A second generation of microfluidic device development began when Materia succeeded in producing several fluorinated norbornene (FNB) monomers. Polymers based on these monomers are resistant to solvents, so microfluidic devices fabricated from them do not require a protective CYTOP coating. In total we received five proprietary monomers in unpurified form, designated by the codes CH39-*nnn*, where *nnn* was 176, 188, 189, 191, or 192. CH39-188 behaved much differently than the others

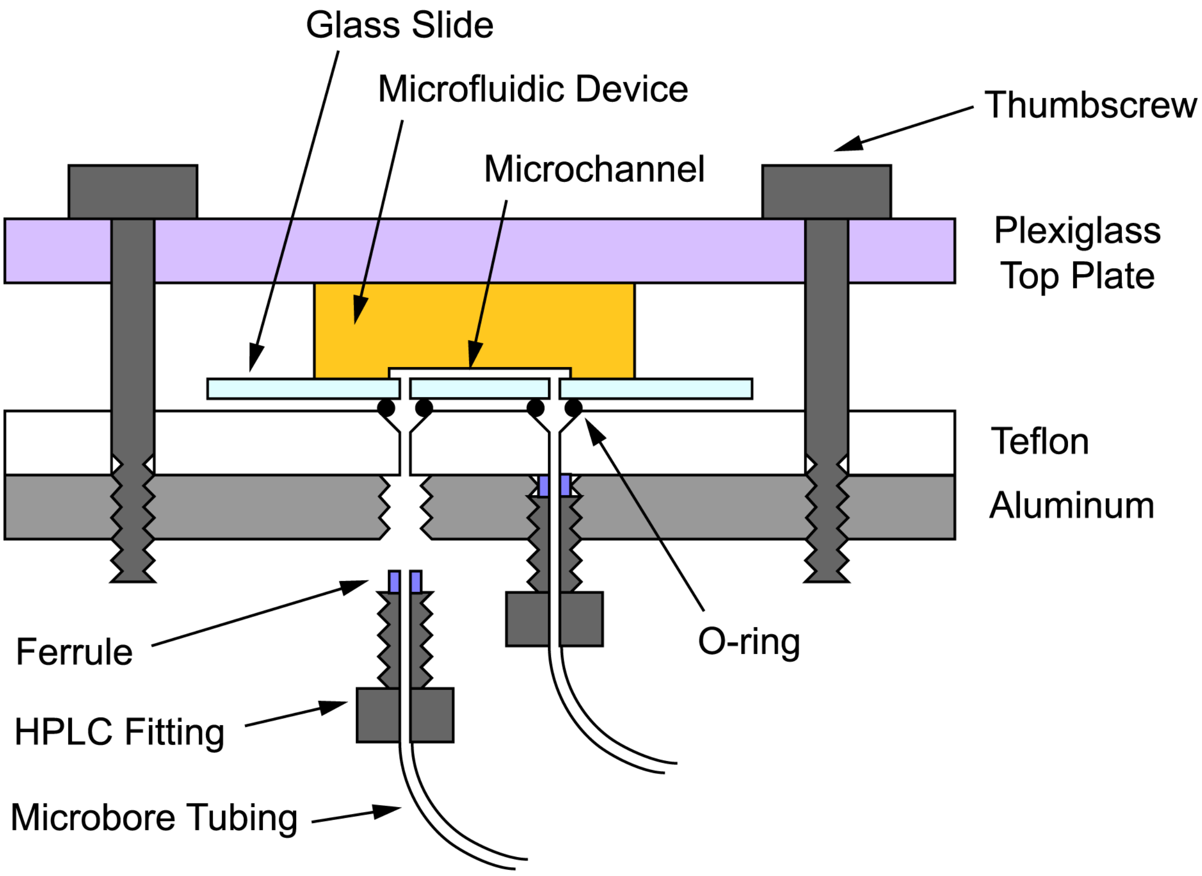

Figure 4.4: **Schematic of fluid delivery jig**. The microfluidic device is held on a glass substrate by sandwiching between bottom and top plates and tightening the thumbscrews. The force applied not only helps adhere the device to the glass, but also helps seal the glass to the O-rings below. Fluids are delivered from microbore tubing by connecting HPLC fittings to the bottom plate. The aluminum part is threaded, and the Teflon part contains only tiny holes; thus the fittings can be tightened against the Teflon to compress the ferrule and achieve a tight seal. Note that fluids are only in contact with the microbore tubing, the ferrule, the Teflon plate, the O-ring, the glass slide, and the channels in the bottom surface of the microfluidic device. The top plate contains large holes (not shown) where connections are made via tubing inserted into the upper surface to pressurize control channels. Also not shown in this figure is the attachment between the Teflon and aluminum plates.

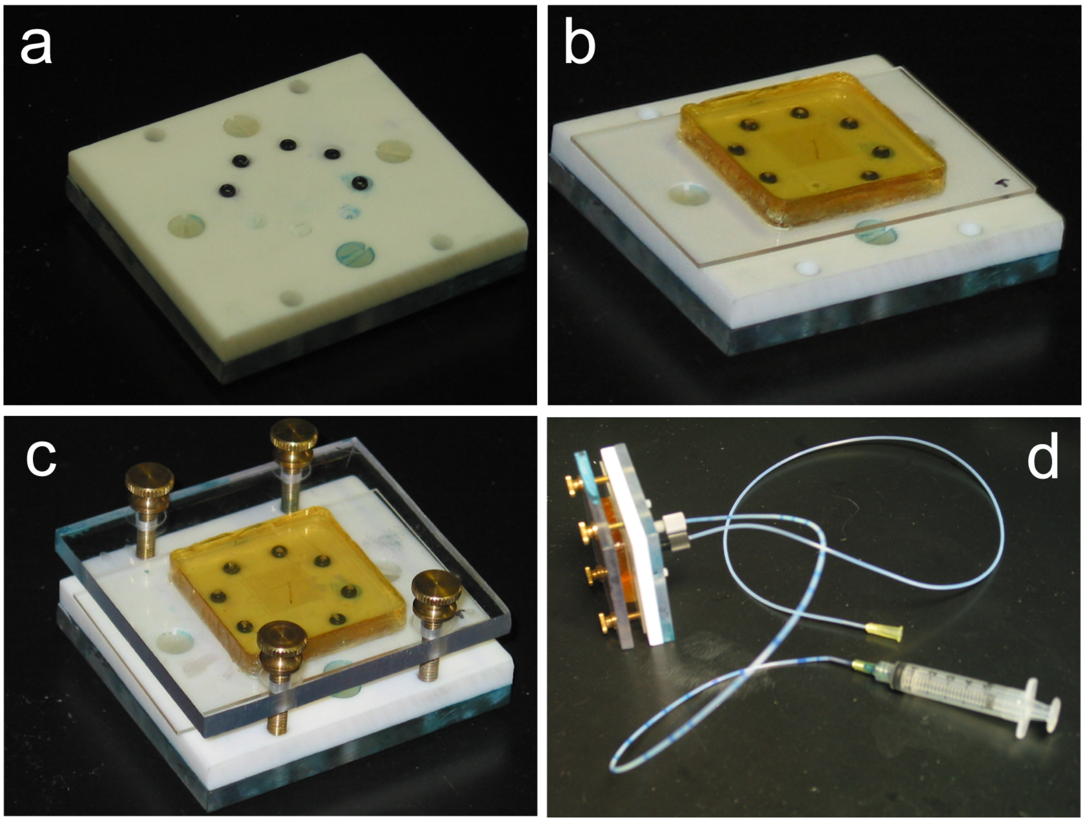

Figure 4.5: **Fluid delivery jig used for testing early Materia devices**. (a) The bottom plate consists of a 3×3 inch Teflon block attached by 4 nylon screws to a matching aluminum block. The pattern of 8 holes in the central region is designed to line up with the fluid inlet ports drilled through the glass slide. A cone-shaped depression is machined at each site to hold in place a black Viton O-ring. The remaining 4 holes are threaded for top plate attachment. (b) A microfluidic device is aligned to a glass slide with holes drilled in positions to match fluid inlets and outlets. (All fluids are delivered through the glass since devices were resistant only on the bottom surface, which was coated with CYTOP or made from FNB.) The holes in the glass slide are aligned with the centers of the O-rings. (c) Next a transparent plastic top plate is attached via thumbscrews threaded into the holes of the bottom plate. The screws are adjusted to press everything together, both to seal the device to the glass slide and to seal the glass slide to the O-rings. Pressure must be applied gently and evenly to avoid deforming or collapsing the microchannel pattern. (d) The aluminum plate contains threaded holes aligned with the fluid delivery holes in the bottom Teflon plate. It is designed to accept 1/4”-28 HPLC fittings with the ferrules tightened against the Teflon block. Fluid is delivered by syringe or by regulated nitrogen pressure.

in terms of colour, wetting properties, and polymerization, suggesting perhaps a problem with the reaction to make the monomer. We worked with the remaining four.

These new experimental monomers were supplied to us in very small quantities, typically 10–20 g (5–10 mL) at a time. Since previous 2-layer devices consumed about 7 g of resin each, we couldn't afford to make entire devices out of fluorinated resin. Therefore, we developed an alternative two-layer approach, wherein the bottom thin layer is made with the solvent-resistant elastomer, while the thick layer is made from non-resistant resin. As with the CYTOP-coated devices, fluids were delivered through holes in the glass substrate to prevent exposure of the non-resistant material to solvents.

We first checked the solvent compatibility of polymers based on these new monomers and then fabricated 2-layer microfluidic devices containing valves and showed they could be operated in the presence of organic solvents.

4.4.1 Solvent compatibility tests

To qualitatively evaluate solvent resistance, we polymerized some thin (appproximately 1 mm) sheets with each of the FNB monomers. Droplets of dichloromethane did not visibly distort any of the materials; however, this solvent rapidly diffused through the sheet of CH39-176 FNB to attack the plastic Petri dish below. We decided not to use this monomer in microfluidic devices because its inability to provide a solvent barrier would likely allow solvents in fluid channels to diffuse through and attack the non-resistant thick layer in our two-material architecture. Sulphuric acid droplets caused no visible effects other than a slight change in surface-wetting properties in the exposed area after many hours (see Figure 4.6b). We attempted to perform long term immersion tests to quantitate polymer swelling in a variety of solvents, but the solvents evaporated so quickly from our small thin samples that accurate measurements could not be made.

Polymers of CH39-189, CH39-191, and CH39-192 seemed to develop significant plasticity and rigidity over time, becoming completely inelastic after about 2–3 days. (This same "aging" effect occurred in our first-generation HNB-ENB-DNB thick-layer formulation, but not in our HNB thin-layer formulation.) 189 was superior in terms of initial flexibility, but 191 and 192 exhibited superior adhesion to glass. For microfluidic device fabrication, however, we were simply limited to using whichever monomer was available at the time. Mixtures of these monomers with CH39-176 at up to 75% loading did not have enhanced flexibility despite the high flexibility and elasticity of polymers made entirely of CH39-176.

In order to confirm *in situ* solvent compatibility in the context of our device architecture, we initially fabricated simplified (1-layer) devices. First, we polymerized a thin layer of FNB sprayed onto a silicon fluid layer mold. We then affixed an aluminum barrier on top of this layer and poured a thick layer of non-resistant resin to fill it. This resin was the same formulation as used for thick layers in our CYTOP-coated devices. These devices contained no control layer and no valves, but were otherwise identical to 2-layer devices. The devices were mounted on drilled glass slides and held in place by our fluid delivery jig (see Figures 4.5 and 4.4). In one experiment, we flowed dichloromethane at 5 psi through a long serpentine channel for approximately 24 h, observing no distortion or deformation of channel features. Upon removal of the device from the wafer, we observed that the material in the vicinity (few hundred microns) of the channel had become somewhat lighter in colour, perhaps due to the extraction of some impurities. (The monomers were supplied to us in unpurified form.) It should be noted, however, that the polymer matrix did not absorb any of the blue dye (xylene cyanol FF) that was contained in our dichloromethane solution. We also applied droplets of sulphuric acid to the bottom of this device and observed that the FNB layer protected the non-resistant thick layer from attack (see Figure 4.6a).

One problem we identified in our fluid-delivery setup was the plastic deformation of the fluid layer near the inlet holes. That is, when we removed the device from the glass slide, a permanent imprint of the edges of the holes was clearly visible. In long-term flow studies this was observed to cause a reduction in flow rate. Since we had observed similar plastic deformation when overtightening the thumbscrews on the fluid delivery jig, we hypothesized that the O-rings (made of Viton) were being swelled by the dichloromethane flowing through them, thus pushing on the glass slide and increasing the pressure with which the microfluidic device and glass slide were pushed together.

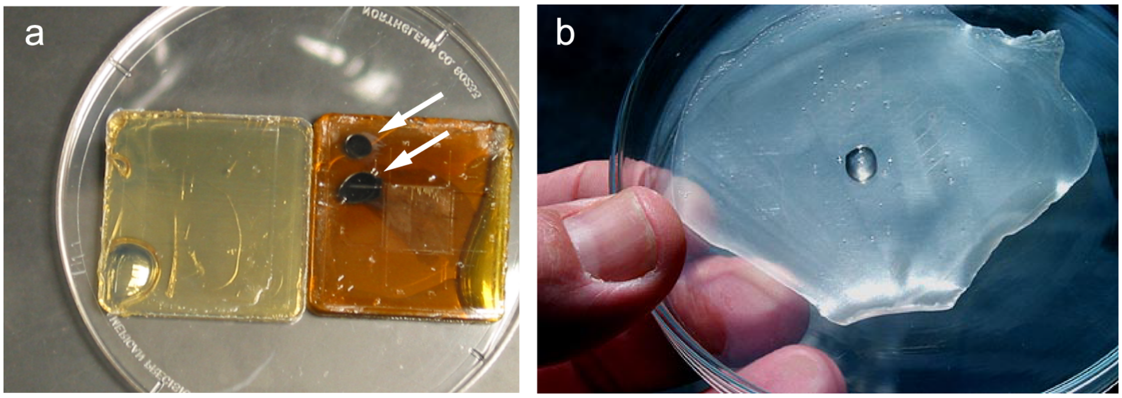

Figure 4.6: **Sulphuric acid resistance of FNB**. (a) Comparison of Materia norbornene device with FNB surface coating (left) and without (right) after exposure to droplets of 96% sulphuric acid. The uncoated device charred immediately, while the coated device was unaffected after many hours. Even after more than 1 year of exposure, one coated device exhibited no visible damage other than a slight change in wetting properties in the exposed region on the surface. Note that the colour difference between devices is simply related to the speed of polymerization. The darker one polymerized slightly more quickly, which generally tends to produce a harder material with higher resistance. The non-resistant norbornene polymer is made with our usual thick-layer formulation (see text). (b) Thin film of FNB CH39-191 unaffected by a drop of acid. This photo courtesy Tony Stephen, Materia, Inc.

This problem was circumvented by devising a new system for fluid delivery using newly available commercial fluidic fittings called NanoPorts, as described below.

4.4.2 Device fabrication

2-layer devices with microvalves were fabricated by a similar procedure to that used for CYTOP-coated devices (except for the coating step). Since only the bottom thin layer was made from solvent-resistant FNB, a push-down valve architecture was again necessary.

Thin layers were prepared by spraying a mixture of catalyzed FNB on a fluorosilanized silicon wafer mold, patterned with fluid channel features. The spray solution was prepared by mixing 4 parts FNB with 1 part of a solution consisting of: 30 mg Irganox, 1 mg C848 catalyst, 5 mg TPP, and 4 g toluene. This formulation results in an initially very flexible and elastic polymer. Spray coating resulted in a wide range of layer thicknesses ranging from 10–100 μm, with huge variation even in a single wafer. However, some spray-coated wafers happened to have the correct thickness and could be used to produce functional microfluidic devices. Unfortunately, the spin-coating method used with the HNB resin for CYTOP-coated devices did not work here: poor wetting of the silicon wafer surface by the FNB resulted in incomplete coverage as the FNB contracted into a small thick pool within seconds after spinning. Thin layers were polymerized by baking for 30 min at 50°C and then for 30 min at 80°C.

One method we tried to better control the layer thickness was to create a barrier wall around the mold pattern with a fixed internal area and to pour a fixed volume of catalyzed resin into this barrier. We attempted this with an epoxy barrier, but observed that the required resin volume is difficult to predict due to the large fraction of resin that collects on the barrier walls. In one set of experiments with a particlar geometry, 500 μL of resin led to layers between 20–80 μm thick; the predicted volume needed for a 30 μm layer was 75 μL. Another difficulty is that an exceptionally level surface is needed inside the oven during polymerization to ensure a uniform coating thickness across the whole mold.

Thick layers were prepared in an identical manner as those for CYTOP-coated devices, differing only by a slight modification of the formulation to reduce the layer rigidity. The revised formulation consisted of 7 g HNB, 7 g ENB, 2.5 g DNB, 45 mg Irganox, 8 mg C848 catalyst, 11 mg TPP, and 0.5 mL toluene.

Bonding was also nearly identical. Catalyst dissolved in toluene was sprayed with an airbrush onto the thin layer (still affixed to the flow-layer mold). Since toluene does not wet the FNB surface, care was taken to allow the toluene to dry after one spray of mist before applying another. Otherwise tiny toluene droplets coalesce to form large droplets that can damage the thin layer by causing pitting. Both layers were then vacuum degassed for 5 min, prior to alignment of the thick layer onto the thin layer. Baking for 30 min at 50°C followed by 30 min at 80°C affords sufficient adhesion so that the 2-layer device can be removed from the fluid-layer mold. Chances of successful bonding are enhanced by synchronizing fabrication steps such that the thin and thick layers are ready for bonding simultaneously. Bonding is possible between these two different materials (FNB and HNB-ENB-DNB mixture) because they share the same catalyst.

The 2-layer device is then bonded to a glass slide containing holes for fluid delivery. Bonding directly to glass is possible, though it is reversible, and the degree of bonding is not the same for all FNB polymers. However, far superior adhesion is achieved by bonding the device to a glass slide coated with FNB. The coating on the slide is applied and cured in exactly the same manner as the thin device layer. After curing, the holes in the glass slide must be re-opened by punching out the plugs of FNB that block them. The microfluidic device is placed onto the coated slide and then baked for 30 min at 50°C followed by 30 min at 80°C. The mounted device is then baked at 50°C overnight to complete the bonding at the two interfaces. It is baked upside-down (with the glass slide at the top) to avoid channel collapse. Note that the brief excursions to 80°C improve bonding by softening the material a little bit, allowing the components to settle together to release bubbles and stress.

4.4.3 Device testing

After device assembly, NanoPort fittings (Upchurch Scientific, Inc., Oak Harbor, WA) were affixed to the glass slide to allow pressurized delivery of fluids into the device. These fittings are glued to the glass surface with epoxy and connect to 1/32-inch microbore tubing via a threaded port and fitting as shown in Figure 4.7. The bottom surface of the NanoPort contains a Kalrez O-ring to protect the epoxy from solvent attack. Though the NanoPorts are supplied with custom cut epoxy rings, they must be baked at 120–140°C for proper adhesion. Since we generally mounted our devices (which cannot withstand this temperature) onto the glass first, we were forced to use 5-minute epoxy. We obtained best results by applying epoxy to the outer ring of the NanoPort shortly after mixing but waiting until it nearly hardened before adhering the ports to the glass. In operation, this new setup is identical to the fluid delivery jig, but the risk of over-compressing the device and causing channel deformation is eliminated.

With all fittings in place, we were able to deliver solvents into the fluid channels under pressure and to pressurize control channels to actuate valves. Though a variety of fabrication difficulties (such as inaccurate fluid-layer thickness and collapsed channels during assembly) resulted in imperfect devices, we successfully demonstrated valve actuation and dead-end channel filling in 2-layer FNB devices.

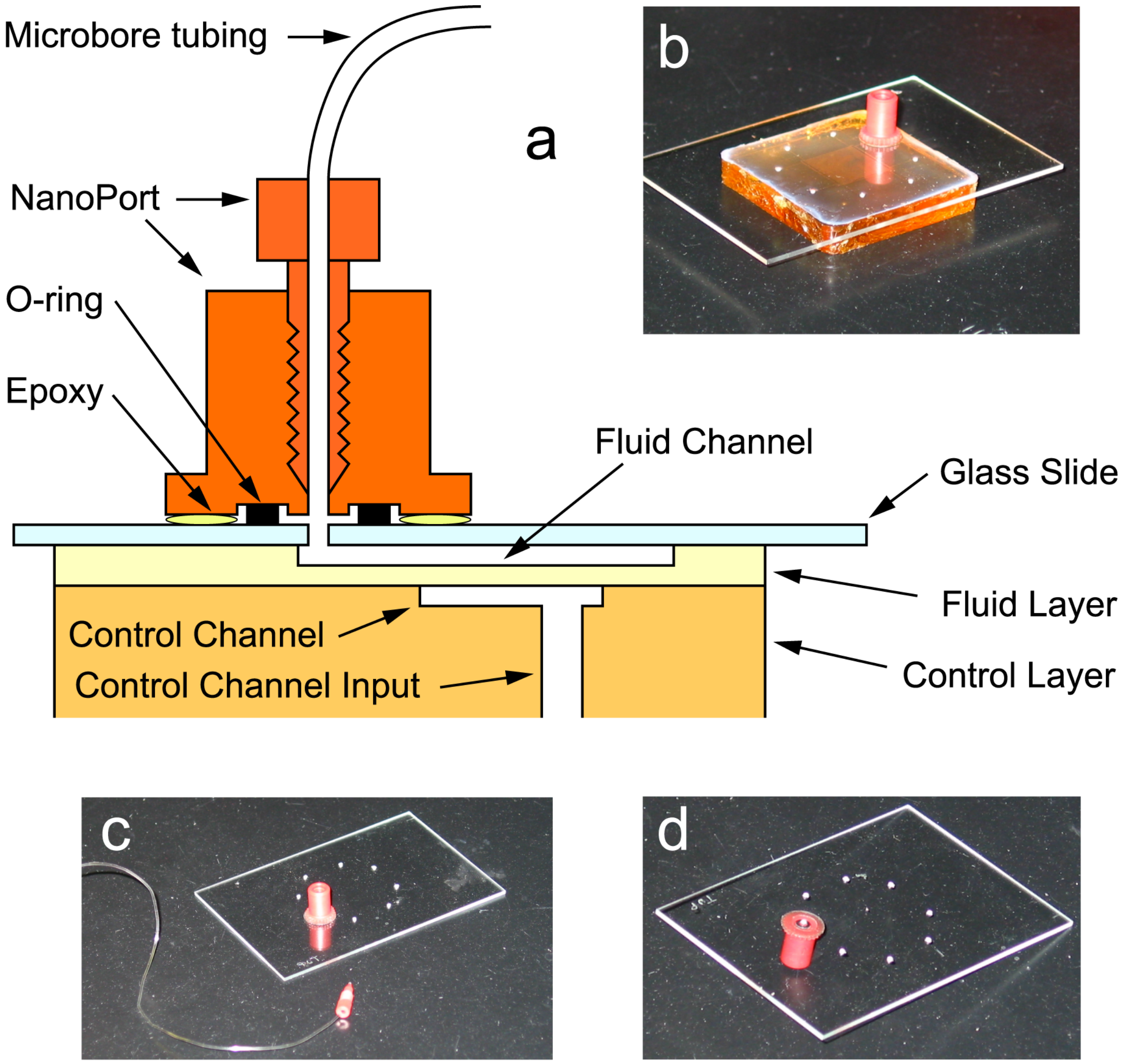

Figure 4.7: **Schematic and photographs of NanoPort connectors**. (a) Schematic drawing of the NanoPort connector. The port is aligned to a hole in the glass substrate and affixed with epoxy. Fluid delivered from microbore tubing contacts only a small part of the NanoPort (made of polyetheretherketone (PEEK) polymer), the Kalrez O-ring, the glass slide, and the FNB (solvent-resistant) layer of the microfluidic device. The control layer can be made of a non-resistant polymer as there is no fluid contact. (b) Photograph of a 2-layer microfluidic device affixed to a drilled glass slide with one NanoPort attached. (c) Photograph of a NanoPort attached to a glass slide with the threaded fitting removed. (d) Underside view of the NanoPort, showing the O-ring and (faintly) the epoxy ring.

In our first working device, containing a CH39-191 FNB fluid layer, we observed a series of valves (controlled by a single control channel) to close after several minutes under a pressure of 12 psi. Materia polymers tend to be quite tacky and most valves remained stuck in the closed position after the control channel pressure was released. Applying 7–8 psi air pressure to the *fluid* channel was sufficient to open all valves after several minutes. NanoPorts were not yet available so solvent delivery was not attempted in this device.

Experiments with another CH39-191 device are shown in Figure 4.8. Bonding of the device to the glass was observed to be sufficient to withstand 5–6 psi of dichloromethane flow for extended periods without signs of delamination or deformation. Though the fluid layer was particularly thick in this device (20–100 μm gradient across the device), one series of valves was partially actuated at 12 psi. Additional pressure could not be applied without causing delamination at the control input pin. Valve actuation was extremely slow due to the thickness and rigidity (due to aging) of the FNB layer.

While this experiment demonstrated long-term *in situ* solvent compatibility and that valves could be actuated completely in FNB devices, the speed of actuation was impractically slow for many applications. With a batch of the more flexible CH39-189 monomer, I successfully fabricated one additional 2-layer device. Flow of dichloromethane at pressures of up to 15 psi was successfully blocked by valves pressurized to 23 psi. With pressurized fluid helping to re-open the valves after closing, I was able to oscillate the valve at rates around 1 Hz. 23 psi control channel pressure and 5 psi fluid pressure resulted in a maximum cyclic actuation rate of 1.3 Hz. The operation of this valve is shown in Figure 4.9. The device happened to contain a couple of collapsed fluid channels, allowing dead-end channel filling to be demonstrated. Due to the permeability of the FNB, the air trapped in a segment of channel several millimeters in length and 10 μm deep was expelled in about 10 minutes by incoming dichloromethane pressurized to 5 psi. Several video frames of this experiment are shown in Figure 4.10. Dead-end filling against a closed valve was also demonstrated.

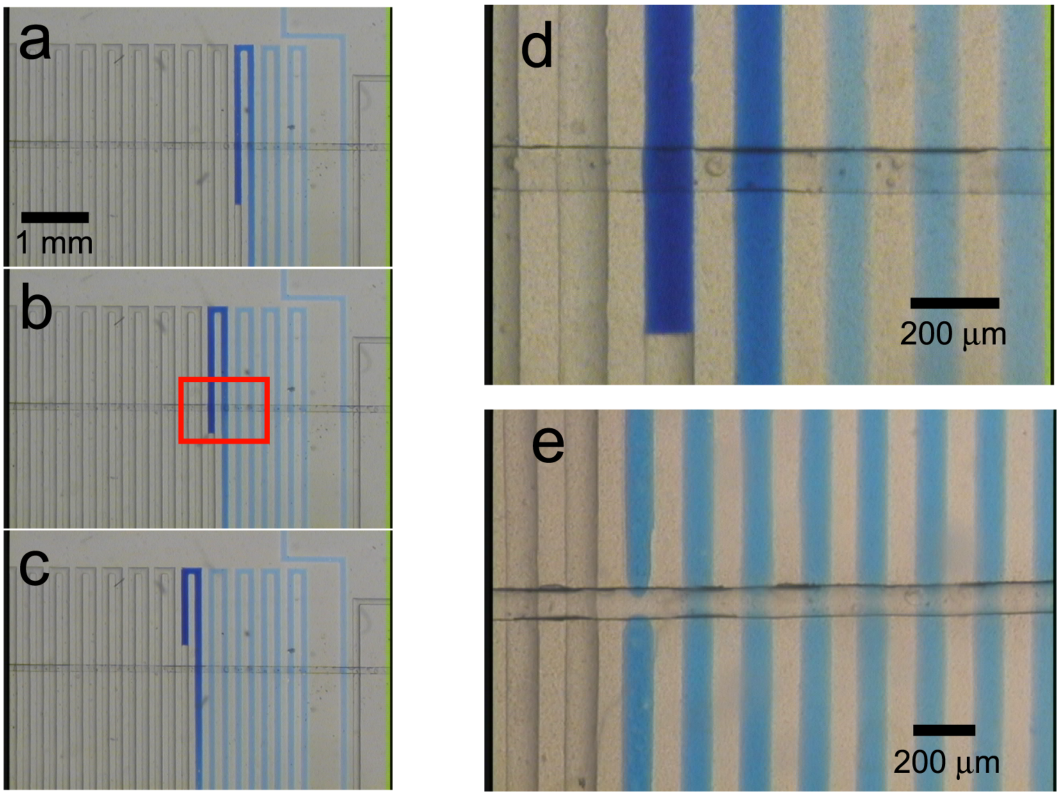

Figure 4.8: **Dichloromethane compatibility and partially closing valves in early FNB microfluidic device**. (a–c) Series of three micrographs illustrating the flow of solvent through a long serpentine channel in an early FNB device. The blue fluid is dichloromethane with some acetonitrile and methanol to dissolve the blue dye xylene cyanol FF. Driven by a pressure of 5–6 psi, it traversed the 16 channel segments (10 μm deep) in several minutes. At the leading edge, the dye is more concentrated, presumably due to evaporation of dichloromethane into the open channel in front, as well as some diffusion into the FNB layer. (d) An enlarged view of the region highlighted in *b*. (e) Partial valve actuation at 12 psi control channel pressure. The control channel is oriented left to right. Valve actuation was incomplete due to the thickness of the FNB layer (20 μm at one side but 100 μm at the other), and was very slow (10 min) due to the aging effect whereby the FNB layer becomes rigid over time. The leftmost blue channel closed completely but periodically leaked. At higher control channel pressures, the device delaminated near the control inlet. The FNB layer was polymerized from monomer CH39-191.

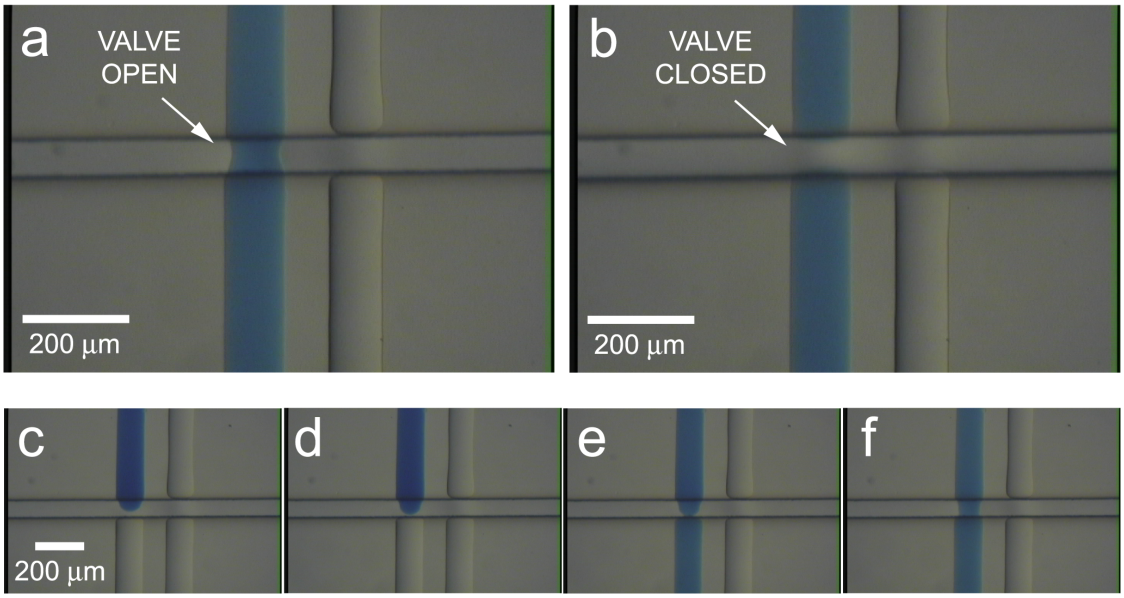

Figure 4.9: **Successful valve actuation in FNB device**. (a) Micrograph of a push-down valve in an FNB device in the open state. The (unpressurized) control channel is oriented left to right, and two fluid channels are oriented top to bottom. The leftmost fluid channel is filled with dichloromethane containing acetonitrile and methanol to dissolve the blue dye xylene cyanol FF; the rightmost channel is filled with air. (b) Same valve in the closed state (control channel 23 psi). The valve was oscillated hundreds of times between these two states with no apparent degradation in performance. With 5 psi fluid pressure, the valve could be actuated at a maximum rate of 1.3 Hz. Up to 15 psi fluid pressure could be applied before bursting the valve open. Note that, due to valve stickiness, the adjacent air-filled channel did not re-open when the control channel pressure was released unless it was pressurized. The device was able to withstand over 30 psi, delaminating only when extremely high pressure was applied via a syringe. (c–f) The same valve forced open by the fluid as the control channel pressure was gradually reduced. Note that when re-opened, the fluid channel remains partly pinched off (smaller width). This is due to the aging effect in the FNB, which gives rise to some platic-like properties. This fluid layer of this device was fabricated from CH39-189 FNB.

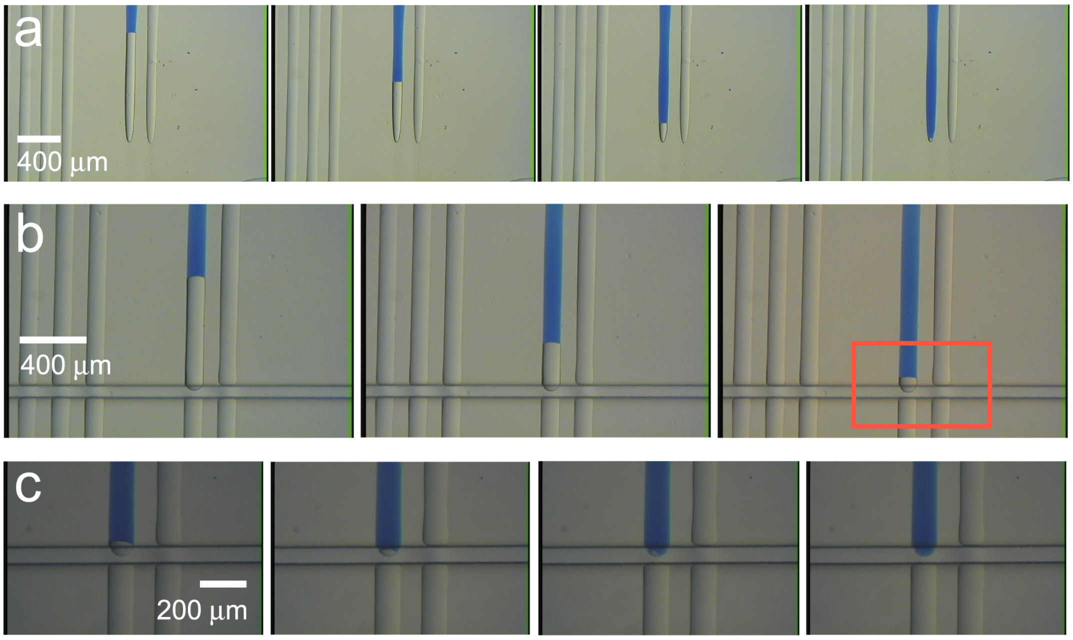

Figure 4.10: **Dead-end channel filling in FNB device**. The device of Figure 4.9 contained some fluid channels that collapsed during device assembly. These provided a convenient means to demonstrate the permeability of FNB by filling a dead-end channel. (a) Series of 4 video images of dichloromethane (dyed blue) filling a collapsed fluid channel. The permeability of FNB is significantly lower than PDMS as it took 4 min for the fluid to fill this short channel segment at 5 psi input pressure. (b) Series of 3 images illustrating dead-end filling against a closed valve (the same as shown in Figure 4.9). (c) Continuation of this series focussed on the region inside the red box.

4.5 Third-generation devices: All FNB

Fabrication of devices from two different materials was necessary to perform our experiments with such limited quantities of resistant materials. In spite of the demonstration of successful devices using this approach and the fact that this architecture minimizes the amount of solvent-resistant (expensive) material needed in a device, two-material devices introduce many complications. Given sufficient quantities of fluorinated monomers, it would be preferable to fabricate devices entirely from a single resistant material (FNB).

One significant advantage would be in making connections to the chip. While NanoPort connectors work, it is difficult and time consuming to drill good quality holes in the glass substrate and to properly adhere each fitting. The epoxy gluing method is not perfect and frequently results in clogging or in an inadequate O-ring seal. In addition, the NanoPorts have a large footprint compared to the hole punching method used in PDMS devices, severely limiting the number of fluid connections that can be made to a single chip. Furthermore, the connectors obstruct the view of the channels below and thus need to be moved to regions of the chip design where observation is not required. A second important advantage is that fabrication of wholly resistant devices permits push-up valve architectures to be used. (In this architecture, the fluid channel is in contact with both device layers.) Push-up valves typically exhibit considerably reduced actuation pressures compared with push-down valves and also enable the fabrication of devices where the fluid layer contains extremely tall features such as large reaction chambers (see [159] supplementary information).

Recently, we have made significant progress towards the goal of fabricating all-FNB devices. Though the supply of FNB is still very limited, experiments using HNB as a surrogate have led to a number of promising strategies to address the difficulty in producing layers with consistent thickness. Several other small improvements in the fabrication procedure have also been achieved.

4.5.1 Towards repeatable layer thickness

In the first two device generations, we had considerable difficulty in producing fluid (thin) layers with a repeatable thickness. Problems primarily stemmed from the extremely low viscosity of the monomer resin that prevents the use of established techniques, such as spin coating, for building sufficiently thick layers.

Recently we have contemplated alternative approaches. For example, the viscosity of the resin could be increased so that spin coating can be performed. One way to do so is simply to allow the resin to begin polymerizing to increase its molecular weight and viscosity and then spin once the viscosity reaches the desired level. However, it is difficult to know when the resin has arrived at a precise viscosity. The polymerization is very sensitive to temperature and, in the vicinity of the viscosity of interest, is also very sensitive to time (see Figure 4.11). Even with carefully controlled mixing times, temperatures, and pipetting and spinning protocols, we observed qualitatively and quantitatively different viscosities from batch to batch. Perhaps there is a way to quantitatively measure the viscosity in real time. If so, the resin can be rapidly cooled once it has arrived at the correct viscosity to maintain it at that level sufficiently long to perform spin coating. Another tactic that Materia has developed is an oligomerization procedure where the resin is polymerized for some time, and then the catalyst is quenched. The viscosity of the resulting oligomer solution is stable over long periods, and the material can be recatalyzed for spinning onto molds. This does seem like a promising approach; however, there is not yet a reliable method to rapidly quench the first polymerization and arrive at a precise desired viscosity. Thus for each new oligomer batch (having a new viscosity), a new spin curve must be generated. Perhaps batches with a desired viscosity can be mixed from batches of higher and lower viscosity. A third method of increasing the viscosity of the resin is to add thixotropic agents. In one experiment we added 50–75 wt% of Cab-O-Sil (Cabot Corporation, Boston, MA), a silica powder, to increase the viscosity of HNB to a level qualitatively similar to Sylgard 184 PDMS prepolymer. However, the resulting cured part had dramatically altered mechanical properties such as rigidity and brittleness, clearly heavily influenced by the high glass content. In principle, one could use microparticles of HNB instead of silica so that the final material properties would not be strongly affected; however, this has not yet been tried.

Another coating method that has been investigated is the “doctor blade” technique, a common industrial method for applying thick films to surfaces. Essentially a blade is moved across the

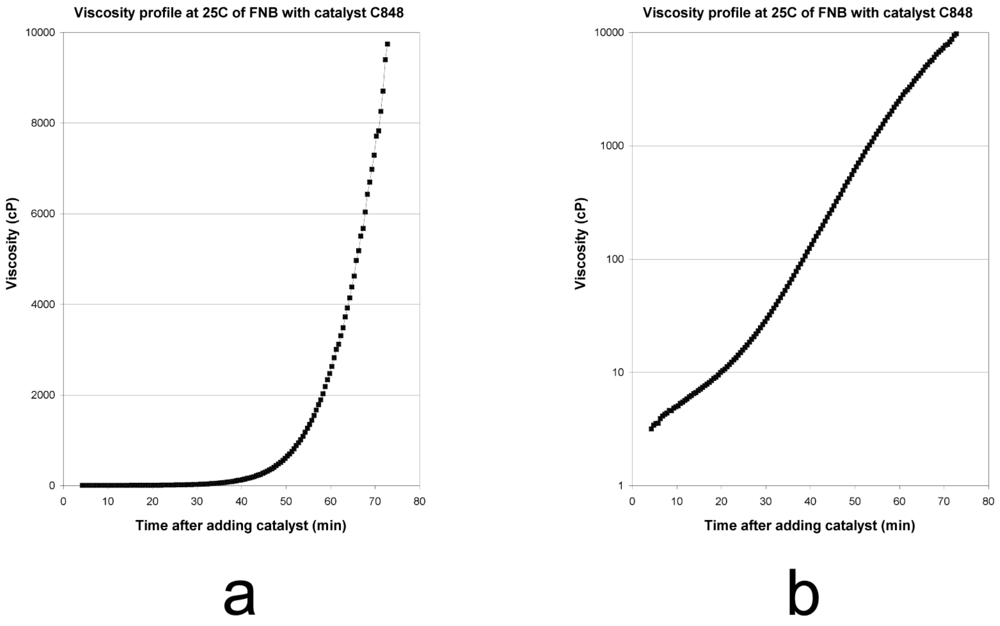

Figure 4.11: **Viscosity profile of purified FNB**. (a) Linear scale; (b) Logarithmic scale. Viscosity was measured as a function of time to monitor the viscosity buildup during polymerization at 25°C of FNB. Approximately 1 mL of catalyzed resin was used from a batch prepared according to the following recipe: 5 mg FNB, 20 mg Irganox, 0.22 mg catalyst C848, 0.67 mg TPP, 0.42 mL dichloromethane. Measurements were made using a cone and plate viscometer (Model AR2000 rheometer, TA Instruments, New Castle, DE) with a 60 mm 1 degree cone at a constant angular velocity of 1 rad/s and shear rate of 57 s^{-1}. One can observe from this data that the slope (rate of viscosity change) is quite high for viscosities of 1000 cP or more that can easily be spin-coated to the needed thickness of 10s of microns.

sample at a fixed height to spread a uniform layer of a viscous coating material over the surface. We had thought that this method might eliminate viscosity dependence and that we could coat from catalyzed monomer (after first allowing it to polymerize/thicken to a qualitatively suitable level), but this was not the case: the coating thickness depends in a complicated way upon the blade height, viscosity of coating material, and other parameters. We have also observed poor repeatability: when tested with PDMS prepolymer we observed 20% thickness variation within a 56 μm coating on a single wafer and 10% variation between wafers. This is consistent with the 0.5 mil (13 μm) tolerance of the unit we used (Universal Blade Applicator, Paul N. Gardner Company, Inc., Pompano Beach, FL) [89].

Lastly, one method that might work with low viscosity monomer resin or oligomer resin is casting between a wafer and a flat surface, a technique that has been used to make thin PDMS membranes [137, 134]. This approach is completely independent of viscosity and seems quite promising.

4.5.2 Additional improvements

Attempts to make devices entirely out of HNB have led to several simplifications in the device fabrication protocol. (i) Resin can be cast on silicon wafers without any surface treatment, eliminating the need for the lengthy fluorosilanization protocol. (ii) Holes can be punched in devices by the same punch machine (Technical Innovations Inc., Brazoria, TX) that is used for PDMS devices. However, we were unable to punch holes manually using Luer stubs. (iii) Use of dichloromethane instead of toluene as a solvent ensures that the antioxidant is rapidly dissolved; thus, no filtering of the resin is required. (iv) Adhesion without catalyst spray provides a strong bond. In one test, a 1-layer HNB device was bonded to an HNB-coated substrate by baking for 3 days at 50°C. The resulting bond showed no signs of delamination when channels were cyclically pressurized between 0–24 psi at 2 Hz continually for 48 h. The first three improvements have been demonstrated to be compatible with FNB; thus, aside from calibrations for shrink factor and parameters related to layer thickness, we expect a smooth transition to the fabrication of all-FNB devices.

4.6 Summary

Through a collaboration with Materia, Inc., we have developed solvent-resistant 2-layer microfluidic devices containing functional microvalves by two different methods. In the first, the thin layer is fabricated from a non-resistant hexylnorbornene polymer with a protective CYTOP coating on the bottom surface. In the second, the thin layer is fabricated from a resistant fluorinated norbornene polymer. Both must use a push-down valve architecture to prevent solvents from coming into contact with the non-resistant parts of the device. We demonstrated long-term solvent (dichloromethane) flow through microchannels, dead-end channel filling, and most importantly, valve actuation. The requirement for a coating on the glass substrate precludes the use of these devices for *in situ* synthesis of compounds on glass; however this affects only a small set of applications.

Given sufficient availability of monomers, it would be preferable to fabricate devices entirely from solvent-resistant FNB. This would greatly simplify the delivery of solvents to devices and expand their usefulness by enabling push-up valve architectures. Significant steps have been made in this direction.

Acknowledgment

Several individuals at Materia played a significant role in this work. I thank Bob Grubbs, Michael Giardello, Mark Trimmer, Chris Harr, Emmanuelle Despagnet-Ayoub, Diana Stoianova, and especially Tony Stephen of Materia for interesting discussions, as well as materials and process development. Tony's tremendous dedication in helping to achieve the successes described herein was unparalleled. Samples of fluorinated materials, as well as loan of equipment (spin coater, air brush, aluminum baking chamber), and generous supplies of non-resistant materials are also greatly appreciated.

I am grateful to my fellow student Saurabh Vyawahare and Isba Silba, a student of Frank Gomez at California State University Los Angeles, for assistance with many experiments that ultimately led to the development of successful fabrication protocols for first- and second-generation devices. Protocols for third-generation devices were developed jointly with Arkadij Elizarov and Young Shik

Shin of Jim Heath's group at Caltech. Matthew Mattson's help with FNB viscosity measurements is greatly appreciated.