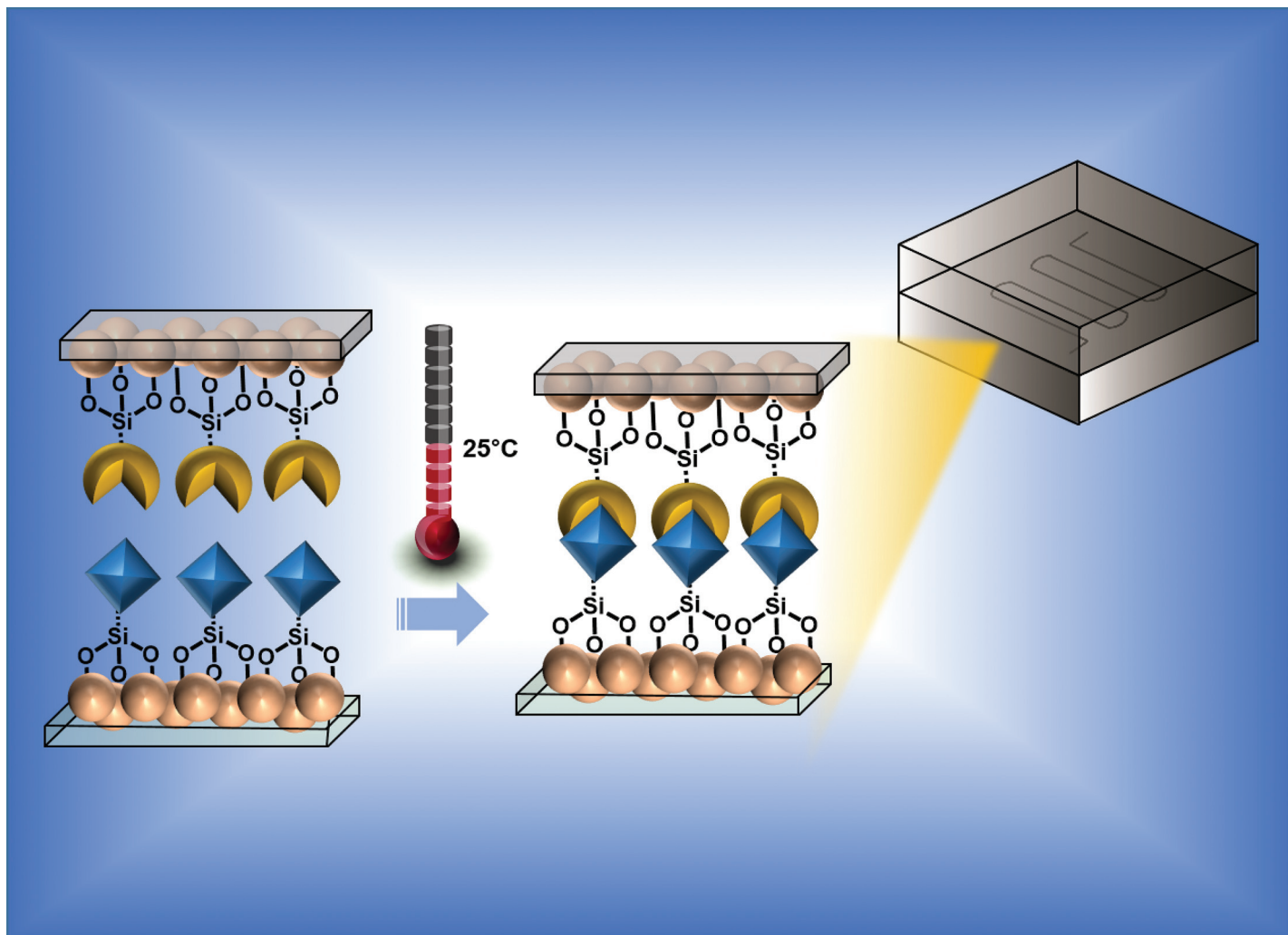


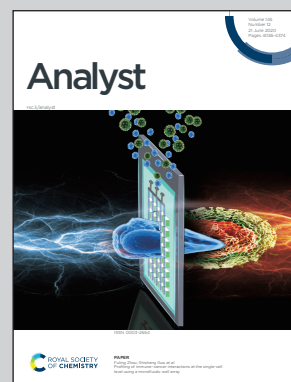


Showcasing research from Professor Nae Yoon Lee's laboratory, Department of BioNano Technology, Gachon University, South Korea.

Microfluidic device fabrication mediated by surface chemical bonding

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TUTORIAL REVIEW

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Microfluidic device fabrication mediated by surface chemical bonding

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This review discusses various bonding strategies for fabricating microfluidic devices, with a special emphasis on the modification of the surface assisted by the use of chemicals to assemble microfluidic devices under mild conditions such as room temperature and atmospheric pressure. The paper includes an overview of the wide ranges of bonding methods used in the fabrication of microfluidic systems, such as anodic bonding, fusion bonding, thermal bonding, solvent bonding, and surface chemical bonding. Among these, surface chemical bonding plays a crucial role between the polydimethylsiloxane (PDMS) and thermoplastics in order to assemble a microfluidic device in a simple and facile manner. The first section reviews relevant research on the sealing for microfluidic devices; in the second section, the materials used for device fabrication are reviewed. The third section discusses the different sealing processes used in the fabrication of microfluidic devices on silicon, glass, thermoplastic, and elastomer. Overall, this review concludes with a discussion on the importance of the surface chemical modification for bonding an elastomer – PDMS – with rigid materials at room temperature under atmospheric pressure and detailed discussions on their bond strengths.

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Introduction

Microfluidics is a prominent field that relies on the knowledge from various fields such as chemistry, physics, mechanics, biology, and medicine.^{1–3} The possibility of a more efficient and feasible analytical testing method has been improved after the discovery of microfluidic systems.⁴ Several substrates such as silicon, glass, and polymers play an imperative role in



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microfluidic technologies, because each substrate has specific microfabrication approaches and certain native properties to create microfluidic devices.^{5–7} Microfluidics is the science and technology of systems that allow small amounts of fluids (10^{-9} to 10^{-18} liters) to be used inside a microchannel with dimensions of tens to hundreds of micrometers.^{8,9} The main advantage of microfluidics is that it reduces the quantity of reagents required for analysis due to the smaller channel dimensions, which leads to smaller sample volumes (femtoliter to nanoliter). Therefore, it can also lead to portable devices for on-site testing that can be used in diverse applications, such as micro-total analysis systems (μ TAS),¹⁰ lab-on-a-chip (LOC),¹¹ actuators,¹² and miniaturized Point of Care (POC) devices^{13,14} that integrate several functions (*e.g.* mixing, sorting, heating/cooling, pumping, sensing, detecting, or analysis) into a user-friendly and cost-effective format.¹⁵

Recently, instead of utilizing silicon-based materials characterized by high cost and incompatibility with biosystems, researchers have started to use polymeric materials to fabricate microfluidic systems.^{16,17} These polymeric materials have several advantages such as transparency, flexibility, low cost, and easy fabrication processes ensuring their wide applicability in constructing microfluidic systems. Polymer materials are divided into two big categories: (1) thermoplastic polymers that are known by their ability to be melted and formed to intended shapes; some of the most influential thermoplastics are polystyrene, polyvinyl chloride, polycarbonate, and poly(methyl methacrylate), which are widely used in the fabrication of microelectromechanical systems (MEMS);^{18–21} (2) thermoset polymer and polydimethylsiloxane (PDMS) that cannot be remoulded or changed into the final shape; this group of polymers is widely adopted for microfabrication processes.^{22,23} The fabrication of microfluidic devices typically involves diverse processes like structural design, mask fabrication, mold fabrication, replication, chip alignment, and bonding.

In the selection of appropriate bonding methods for the fabrication of microfluidic devices, different issues such as bond strength, interfacial stress, microchannel accuracy, solvent compatibility, surface chemistry, and optical transparency should be considered. There are several techniques such as thermal bonding,²⁴ solvent bonding,²⁵ plasma activated bonding,²⁶ and ultrasonic welding.²⁷ These techniques have been reported for bonding different functional polymer sub-

strates used in the production of plastic-plastic devices; however, these methods will not be adopted preferably for microfluidic fabrication, because they require high temperatures and efficient polar and nonpolar solvents for bonding, leading to the deformations of the microchannel. Furthermore, in oxidation bonding, silanol (Si–OH) groups are introduced on the surface of PDMS by using oxygen plasma or corona discharge.^{28,29} This surface modification results in an irreversible bonding, through the formation of siloxane bonds (Si–O–Si), providing a simple and stable bonding procedure. However, the bonding step must be completed within minutes after the oxidation pre-treatment to prevent its recovery to hydrophobicity which lowers the surface free energy (SFE); this method is not suitable to non-silicon-based materials, such as thermoplastics. Another bonding method, adhesive bonding, is one of the most common fabrication methods that yield a high bond strength of microfluidic devices. For example, a thin PDMS layer can act as an adhesive for bonding two polymer substrates;^{30,31} however, it is difficult to estimate an exact volume of a liquid present in the inside of microchannels because it can block the microchannels. Similarly, in another study, a partially cured PDMS as an adhesive layer for bonding PMMA was reported;³² however, the liquid adhesives can clog the microchannels, which can adversely affect the microfluidic systems. To overcome these issues, the surfaces of two polymeric substrates need to be modified and come to a conformal contact with each other to achieve successful bonding, preserving channel integrity and high bond strength.

In fact, the strong hydrophobic nature of PDMS will not bind any other polymeric substrate without modification of the surface. Therefore, surface modification is necessary, and the surfaces of the PDMS, as well as the thermoplastics, are modified using different chemicals that do not require high pressure or temperatures to create high strength microfluidic devices (Fig. 1). This surface chemical modification technique is robust and can be applied to silicon-based materials, polydimethylsiloxane (PDMS),³³ and non-silicon-based thermoplastic substrates such as poly(methyl methacrylate) (PMMA),³⁴ polycarbonate (PC),³⁵ and polystyrene (PS).³⁶

Here, we review and discuss on various fabrication methods currently used in the microfluidic field. We focus on methods used to produce irreversible sealing of microfluidic devices *via* surface chemical modification of the substrates that can allow

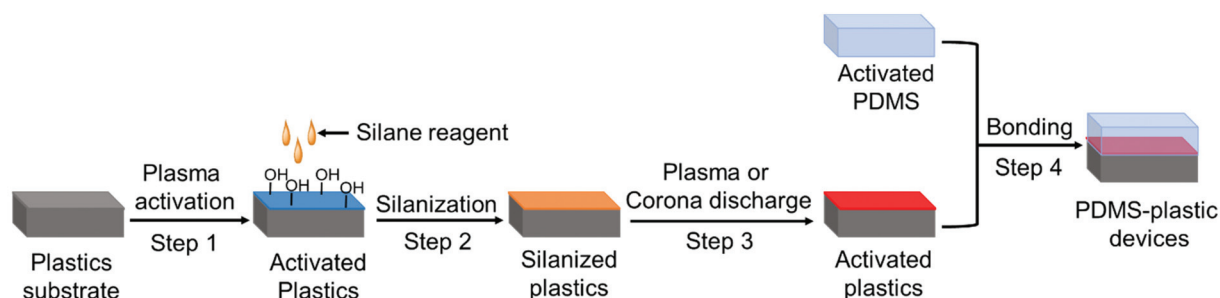


Fig. 1 Schematic representation showing the irreversible bonding between PDMS and thermoplastics.

the high-pressure fluid input, since this ensures robust bonding of the microfluidic devices. To the best of our knowledge, despite the important role of the surface chemical bonding technique, none of the previous reviews has focused on it. Moreover, this review focuses on different bonding methods on silicon, glass, thermoplastics, and elastomers. In this study, we prioritize surface modification of PDMS and rigid materials by using chemicals to obtain permanently assembled microfluidic devices and examine their bond strengths in detail.

2. Materials for the fabrication of microfluidic devices

In adopting a design or material for a microfluidic device, the following three main criteria should be considered: the degree of integration, function, and utilization. In addition, while addressing the suitability of materials to design the microfluidic devices, various physical characteristics such as flexibility, gas permeability, electrical conductivity, compatibility of solvents, and optical transparency should be acknowledged.

Silicon and glass substrates were initially used as materials for microfluidic device; later, as the field advanced, other materials were also introduced. These materials are divided into the following three categories: inorganic, elastomer, and thermoplastics. Advantages and disadvantages of these materials are described in Table 1.

2.1. Inorganic materials

2.1.1. Silicon. Silicon was the first material adapted to design microfluidic devices.³⁷ The structures on silicon for microfluidic devices are created *via* either additive methods (such as metal or chemical vapour deposition) or using subtractive methods (*e.g.*, wet or dry etching).⁶ The elastic modulus (130–180 GPa) of silicon is very high, and it is difficult to make high-performance microfluidic devices such as valves and pumps. The introduction of silanol (–Si–OH) group on the surface of the silicon is well developed, so modification is easily attained *via* silanes which was used in various

biological applications.^{38,39} Moreover, silicon is opaque to visible light, but transparent to infrared. This drawback can be overcome by introducing transparent substrates (glass or polymer) other than silicon in a hybrid system.^{40,41}

2.1.2. Glass. In the fabrication of microfluidic devices, glass emerged as the material of choice after the initial focus on silicon, and wet or dry etching methods were used to create microstructures on the glass.⁶ In glass, thermal fusion bonding is widely adopted for sealing, and the performance of the channels will be influenced by temperature pre-treatment. For that reason, the surface of the glass requires frequent cleaning and polishing. In addition, glass is biocompatible, has low nonspecific adsorption, and is gas impermeable.

2.2. Polymers

In the past 15 years, polymer-based materials have been used to fabricate microfluidic devices, as this approach offers great flexibility in selecting suitable materials with specific properties for designing microfluidic devices.⁴² Polymers are extensively used in microfluidic devices fabrication due to their affordable price and easy accessibility. In addition, polymer materials typically used in microfluidic applications can be classified into two major branches based on their physical properties: elastomers and thermoplastics.

2.2.1. Elastomers. PDMS has been primarily used in microfluidic devices as a substrate since 1990. Recently, academic laboratories have used PDMS in the development of PDMS-based microfluidic devices. PDMS is characterized by easy availability, acceptable price, and rapid fabrication.⁴³ More importantly, the liquid PDMS prepolymer can be cured *via* thermal treatment at moderate temperature (40–70 °C) and casting with a nanometer solution using photoresist templates.⁴⁴ In addition, preparing these templates is easier and inexpensive as compared to the preparation of silicon or glass templates, and it is easy to peel PDMS off the templates after being cured due to its low surface energy. PDMS chip can be sealed reversibly and conformally with another piece of PDMS, glass, or other materials through a simple contact of the surfaces. Also, it is very convenient to irreversibly bond

Table 1 Comparisons of three types of materials used for fabricating microfluidic devices

Materials	Advantages	Disadvantages
Silicon and glass	• High resistance in organic solvents • Stable electroosmotic mobility • High thermal conductivity • Precise fabrication of microchannel	• High fabrication cost • Low gas permeability • Complicated fabrication procedure • Complicated strategy for bonding
Elastomer	• Low fabrication cost • Easy surface modification • High elasticity • Simple and fast bonding	• Incompatible with organic solvents • Adsorption of biomolecules • Water permeable • Difficult for mass production
Thermoplastics	• High mechanical strength • High optical transparency • Inexpensive • Low moisture absorption	• Poor resistance in specific organic solvents • Difficult for surface modification • Difficult to fabricate microvalve • Difficult to assemble under mild conditions

two PDMS, PDMS to silicon, or PDMS to glass, using the oxidation of PDMS surface by plasma or a thin layer of PDMS acting as a glue.⁴⁵ PDMS microfluidic devices are widely used in bio-related research, such as cell screening, cell culture, and biochemical assays.^{46,47} In particular, the efficiency of PDMS in handling a very small quantity of liquid such as picoliter and femtoliter makes it an excellent tool for single-cell analysis.⁴⁸ PDMS is also gas permeable which is necessary for long-term cell culture in sealed microchannels. In contrast, other substrates such as silicon, glass, and thermoplastics are not applicable for this purpose. However, a limitation of PDMS lies in the formation of bubbles due to its gas-permeable nature.

2.2.2. Thermoplastics. It is a polymeric material that becomes pliable or moldable when heated to reach the glass transition temperature (T_g) and solidifies upon cooling.⁴⁹ When the temperature is increased, the polymer chains associated with intermolecular forces are weakened, and subsequently, yield a viscous liquid. At this condition, thermoplastics are used to produce different shapes of structures by various polymer processing methods, such as injection molding and compression molding.^{50,51}

2.2.2.1. Poly(methyl methacrylate) (PMMA). Poly(methyl methacrylate) (PMMA) is normally synthesized through the polymerization of methyl methacrylate, and patterns can be created by injection molding or hot embossing. In terms of stability, chemical compatibility, and optical transparency, PMMA is a good material for the progress of thermoplastic microfluidic networks.⁵² PMMA has the elastic modulus of 3.3 GPa and a good optical transparency from the visible into the UV wavelength.⁵³ It can be altered to improve its resistance for alkali, acid, and organic solvents, and the wettability of the PMMA surface has been modified by various approaches.⁵⁴ Despite this progress, the deformation of PMMA channels upon long-time exposure to organic solvents and high temperatures confines its further use.

2.2.2.2. Polystyrene (PS). Polystyrene (PS) is an aromatic hydrocarbon polymer synthesized from the polymerization of styrene.⁵⁵ Generally, PS is solid form at room temperature (RT), but melts when reaching its T_g at approximately 100 °C. At this point, it can be moulded to produce the appropriate shapes.⁵⁶ Plasma oxidation or chemical modification method is necessary to change the hydrophobic surface of PS to a hydrophilic surface.⁵⁷ In addition, PS containing microfluidic devices is very promising for cell culture application and could overcome the disadvantage of PDMS-based microfluidic devices, because non-specific adsorption of biomolecules on the surface is a major drawback of PDMS.^{58,59}

2.2.2.3. Polycarbonate (PC). Polycarbonate (PC) is synthesized through the polymerization of bisphenol A and phosgene to form the repeating unit of carbonate groups. PC has various advantages including low moisture absorption, high resistance, and excellent T_g (~145 °C). Accordingly, PC has been chosen particularly for a polymerase chain reaction.⁶⁰ However, the poor resistance to specific organic solvents and UV absorption are the main drawbacks for PC.

3. Sealing techniques

Sealing is a critical step in the fabrication of microfluidic devices. Major problem resides in achieving easy and high strength bonding due to the weak interactions between the substrates like silicon, glass, elastomer, and thermoplastic. Poor bonding results in air bubble formation between the bonded surfaces leading to leakage and damage to the quality of microfluidic devices. Therefore, many studies seek to develop robust sealing techniques that would remarkably advance their commercial viability. Accordingly, the remainder of the present review is targeted for investigating sealing techniques and is divided into three main sections; bonding between (1) hard surfaces such as silicon and glass, (2) non-conformal polymers, and (3) PDMS with rigid surface materials.

3.1. Sealing methods for hard surfaces such as silicon and glass

3.1.1. Fabrication of channels in hard surfaces. The fabrication of microchannels and structures is the primary part of the fabrication of microfluidic systems. Micromachining of silicon and glass is still interesting for several applications, and the etching method is the most common technique for channel fabrication.^{61,62}

3.1.2. Bonding methods. Anodic bonding is used to seal the structured silicon made by wet or dry etching methods with the use of plain glass cover. During anodic bonding, the high voltage (between 200 and 1000 V) and high temperature (between 180 and 500 °C) are required. Under these conditions, ions in the glass rapidly move towards the cathode, resulting in a large electric field at this interface and pull the two surfaces – silicon and glass – closer. On the other hand, glass is a potential candidate for microfluidic and nanofluidic devices due to its good chemical compatibility, temperature stability, and optical transparency. Furthermore, another alternative is glass-glass fusion bonding that helps to achieve a higher bonding strength as compared to anodic bonding. The details of bonding methods and their disadvantages are discussed below.

3.1.2.1. Anodic bonding. Lopez-Martinez *et al.* fabricated a novel and versatile transparent micropipette for biological applications by creating a sealing between the silicon and glass.⁶³ In this method, photolithography and deep reactive-ion etching (DRIE) processes were used for channel fabrication. After the channel formation, both glass and silicon wafers were placed on a hot plate; then, the temperature was gradually increased from 40 to 400 °C. Afterwards, 100 V was applied between the silicon and glass wafers for 30 min, maintaining the silicon wafer at a positive bias to form the anodic bonding. In another study, Kaigala *et al.* created a minor modification on the above technique: specifically, the silicon surface was bonded with a glass wafer at 450 °C, and 1250 V was used instead of 100 V.⁶⁴ Furthermore, the same technique was adopted for fabricating the microfluidic devices for use in different applications.^{65–68}

3.1.2.2. Plasma activated bonding and fusion bonding. Howlader *et al.* described the glass-glass wafers bonding by adopting the sequential plasma activation process (SPAP), and the bonding experiments were conducted in the atmospheric air of a class 10 000 cleanroom.⁶⁹ Furthermore, several other studies investigated the bonding between the glass substrates at RT/low temperature using reactive ion etching (RIE) plasma treatment with a variety of gas sources such as oxygen/tetrafluoromethane.^{70–72} The same procedure was adopted for silicon wafer for surface activation based on the annealing temperature up to 600 °C for bonding.^{73,74} Furthermore, Allen *et al.* and Yuen *et al.* reported on using calcium-assisted glass-glass bonding technique which requires the washing of the glass surfaces with aqueous calcium(II)acetate solution; in these studies, uniform bonding was obtained while two glass slides were clamped between two binder clips and maintained in an oven for 2 h at 115 °C.^{75,76} Similarly, sodium silicate solution was used to produce a defect-free microfluidic device fabricated by glass/metal/glass substrates.⁷⁷ Kuo and Lin have proposed a thin glass substrate containing channel that was thermally sealed with a blank glass coverslip at 580 °C for 8 h.⁷⁸

Furthermore, Huang *et al.* bonded two glass substrates to fabricate the microchip with high bond strength when the temperature was increased up to 560 °C.⁷⁹ Recently, Koppaarthi and Crews have reported a novel method for simple and rapid fabrication of microfluidic devices using a household microwave oven at the temperature ranging from 590 to 870 °C.⁸⁰ Mahmoodi *et al.* described a quick method to fabricate large glass micromodel networks; the proposed method requires heating the glass plates up by 5 °C per minute and maintaining them at 610 °C for 4 h.⁸¹ The parameters used for sealing hard substrates are summarized in Table 2.

3.1.2.3. Limitations. The direct bonding of silicon and glass produced a high-strength bond. However, the wafers were fused during direct bonding, and in order to prevent the thermal stress, a slow cooling process was initiated, even though the wafers were either cracked or broken. Furthermore, cleaning the organic and inorganic residues from the wafers is still a tedious task for achieving good, void-free bonding, which is a major drawback of these techniques. In addition, these techniques require extremely clean surfaces, clean room conditions, specialized equipment, and high temperature for bonding (typically above 500 °C). Due to the limitations exhibited by silicon and glass used as substrate materials in the fabrication of microfluidic devices, there is an urgent need to change from those materials to the low-cost and easily avail-

able polymeric PDMS and thermoplastic materials whose use is now indispensable in microfluidics.

3.2. Sealing methods for non-conformal polymers

3.2.1. Fabrication of channels in thermoplastics. The fabrication of micro/nano-sized structures on thermoplastics are crucial task for both academic and industrial research efforts to meet the growing demand for device miniaturization needed in various applications. Consequently, injection molding, hot embossing, and UV-imprint lithography are the most widely used methods for patterning of micrometer and sub-micrometer-sized structures on the thermoplastics.^{82,83}

3.2.2. Bonding methods. Among the important methods developed for thermoplastic microfluidic devices, there are various bonding methods, such as thermal fusion bonding, solvent bonding, ultrasonic welding, and bonding after surface treatment. The bonding methods and their disadvantages are discussed below.

3.2.2.1. Thermal fusion bonding. During the thermal fusion bonding, the integrity of microchannel, bonding area, and required strength after the bonding must be considered, and these characteristics are responsible for the quality of the microfluidic device.⁸⁴ Shadpour *et al.* fabricated a 16-channel PC functional microfluidic device using PC substrates. Following the channel fabrication, the PC microdevice was clamped between glass plates, and was maintained in a gas chromatography (GC) oven for 20–30 min at 155 °C for thermal bonding to occur.⁸⁵ Similarly, Park *et al.* reported a leak-free sealing of PC by thermal fusion bonding at 150 °C for 30 min. Leakage of the device was verified by using a fluorescent dye, and the deformation of microstructure was also examined by visual inspection using a microscope.⁸⁶

In thermal bonding, the bonding temperature and fabrication time can be reduced with the application of external pressure. For instance, in the study of Wang *et al.*, the PC cover plate containing gold electrodes and the PC substrate with microchannel structures were sandwiched between two glass plates at the temperature of 128 °C with the pressure of 0.1 MPa for 2–3 min using a homemade thermal press system for thermal bonding.⁸⁷ Likewise, Nie and Fung has fabricated a PMMA multichannel microfluidic device at the temperature of 97 °C for 15 min with the pressure of 0.6 MPa using a thermally controlled hot press.⁸⁸ In addition, Du *et al.* introduced PMMA-PMMA thermal bonding at 91 °C under 1.4 MPa for 360 s, and the experimental results showed an improvement in the effective bonding area and an increase in the bonding quality.⁸⁹ In contrast, Tan *et al.* demonstrated a novel thermal

Table 2 Summary of techniques used for bonding hard surfaces and their parameters

Method	Materials	Process parameters	Application	Ref.
Anodic bonding	Glass/silicon	400 °C, 100 V, 30 min	Biological application	63
		450 °C, 1250 V	Biological application	64
Plasma activated bonding	Glass/glass	O ₂ /N ₂ plasma activation, 60 s, 30 Pa	NA	69
Fusion bonding	Glass/glass	Aq. calcium acetate, 115 °C, 2 h	Capillary electrophoresis (CE)	75 and 76
		580 °C, 8 h	Biomolecule detection	78

direct bonding for PMMA involving the high temperature with low pressure instead of low temperature/high pressure method to maintain the structural integrity of microchannels on PMMA.⁹⁰ In this technique, the PMMA stack was heated to 165 °C and the pressure less than 20 kPa was applied for 30 min to produce a microfluidic device.

Moreover, Fan *et al.* studied the thermal bonding technique for PMMA to PS applying temperature from 110 to 125 °C with the compression force from 0.36 to 0.51 MPa.⁹¹ Chen *et al.* successfully fabricated the PMMA-based four-layer microfluidic chip by adopting the same bonding technique, which has a bond strength of 1.3 MPa.⁹² In a recent study, Mahmoodi *et al.* described a gas-assisted thermal bonding (GATB) for sealing PMMA surfaces at elevated temperature to make microfluidic devices with low distortion.⁹³ In this method, pressurized gas was applied to two substrates, forcing them to bond together. Furthermore, the bonding temperature was 170 °C, and the gas-assisted thermal bonding resulted in less distortion in microchannels as compared with the conventional hot pressing method. Also, the molecular weight of polymers plays a key role in the bond strength of microfluidic devices fabricated using the thermal bonding method. For example, Nayak *et al.* investigated the thermal bonding between PMMA layers of different molecular weights.⁹⁴ The results showed that the PMMA pairs between the molecular weights of 350 and 996 kDa achieved the greatest bond strength of 1.589 ± 0.286 MPa.

3.2.2.2. Solvent bonding. Solvent bonding is another inexpensive, simple, and rapid technique to combine microfluidic parts produced from the thermoplastic polymers that give a high bond strength and an excellent optical transparency. However, the selection of appropriate solvents and curing conditions play a significant role in producing a successful bond without clogging microchannels. Sun *et al.* developed a method for rapid prototyping PMMA containing microfluidic devices using acetonitrile as a solvent.⁹⁵ In this study, a PMMA cover plate was reacted with acetonitrile for 2 min followed by bonding with microchannel-imprinted PMMA at RT for less than 15 min. Likewise, a novel method for fabricating PMMA-based microfluidic devices using a low azeotropic solvent composed of ethanol diluted with 1,2-dichloroethane was proposed by Lin *et al.*⁹⁶ In this method, the bonding was accomplished at RT for 7 min, and the deformation of the microchannels was avoided because the sealing was processed at RT.

Water can act as a sacrificial layer to avoid channel deformation and was used to attach the two polymeric substrates during the solvent bonding. Therefore, this concept was applied to fabricate PMMA microfluidic device where dichloromethane (DCM) was used as solvent.⁹⁷ In another method, Umbrecht *et al.* fabricated the PMMA microfluidic device using ethylene glycol dimethacrylate as the solvent, and this method yielded a high bond strength (3.5 ± 0.8 MPa) with less channel deformation.⁹⁸ Tran *et al.* reported a simple, robust, and rapid approach to bond PMMA–PMMA using ethanol treatment followed by UV irradiation.⁹⁹ A strong interaction between the ester group of PMMA and hydroxyl group of

ethanol resulted in permanent sealing in less than 1 min under the UV treatment ($\lambda = 234$ nm), and 90% of ethanolic solution was used to produce the highest bond strength of approximately 6.17 MPa.

The introduction of pressure for the bonding of the substrates could help to avoid the application of high temperature for the fabrication of devices. Based on this concept, 75% of acetone was added to the PMMA surfaces and placed on a pre-heated hot plate for 20 min at 40 °C with the pressure of 103 kPa to facilitate bonding.¹⁰⁰ Similarly, Ng *et al.* used isopropanol (IPA) to realize bonding of PMMA microfluidic chips at 80 °C under 2.67 bar for 30 min.¹⁰¹ Hsu and Chen has fabricated an ethanol-assisted PMMA microfluidic device by heating at 100 °C for 9 min under 0.25 kg cm^{-2} to produce a high bond strength with less distortion in microchannel morphology.¹⁰²

Moreover, Bamshad *et al.* studied a thermally solvent-assisted bonding at 68 °C for less than 15 min.¹⁶ This method also compared the use of two solvents – ethanol and IPA – in the bonding performance and ensured that permanent bond was realized without deformation or leakage in the channels regardless of the solvent used. Recently, Faghieh and Sharp has studied a different mixture of solvents and different temperature ranges for fabricating PMMA–PMMA microfluidic devices.¹⁰³ The results showed that the solvent mixture of 80% IPA and 20% DCM bonded at 70 °C for 5 min resulted in the highest bond strength with approximately 4.2 MPa. Apart from PMMA devices, another study fabricated a PS microfluidic device using acetonitrile as the solvent at 80 °C for 2 h.¹⁰⁴

3.2.2.3. Ultrasonic welding. Ultrasonic welding technique, which was first reported to produce MEMS devices in 2006, is believed to be attractive for the thermoplastic joining process.¹⁰⁵ Ultrasonic welding offers low temperature and short bonding time, so it is particularly well adapted for the fabrication of thermoplastic microdevices. Li *et al.* presented a novel, easy, and low-temperature bonding for PMMA microfluidic device in the ultrasonic field.¹⁰⁶ In the experimental setup, PMMA substrates were fixed with clamps and bonded by applying ultrasonic with the intensity of about 0.05 W cm^{-3} . Similarly, Luo *et al.* described the bonding of PMMA microfluidic device by both thermal-assisted and solvent-assisted ultrasonic bonding with the bonding time of 30 and 20 s, respectively.¹⁰⁷ Likewise, Zhang *et al.* conducted the experiments to make a PMMA multilayer microfluidic device using thermal-assisted ultrasonic bonding, and the method was applied for bonding multilayers of poly(ethylene terephthalate) (PET) and cyclic olefin copolymer (COC).¹⁰⁸ Poulsen *et al.* successfully bonded COC–COC microfluidic device using an ultrasonic welder by applying 25 J of 75% vibrational amplitude, 400 N of trigger force, and 0.5 bar of vertical welding pressure.¹⁰⁹

3.2.2.4. Surface modification. Another frequently used low-temperature bonding method is surface treatment for bonding. In fact, thermoplastics are generally low in surface energies that limit the strength of the bonding between the mating substrates. To overcome this limitation, the formation of electrostatic interactions leads to a high surface energy

which can produce strong covalent bonds across the interface. Introduction of pressure to the substrates plays a key role in this method. Tsao *et al.* described low-temperature bonding of PMMA and COC using surface treatment by UV/O₃ with the pressure of 4.8 MPa for 10 min and the temperature ranges of 25–110 °C.⁵³ Similarly, Hu *et al.* developed a PMMA microfluidic device using a UV light for 2 h, and the assembly was placed in an oven at 45 °C under the pressure of 1.19×10^5 Pa for 35 min.¹¹⁰

In several methods, some chemicals were used to activate the surface of the thermoplastics. Liu *et al.* successfully employed UV/O₃ for surface treatment followed by reaction with an aqueous solution containing 0.6% of 3-(trimethoxysilyl) propyl methacrylate (TPM) and 0.1% of HCl for PMMA bonding at 85 °C with the pressure of 500 psi for 15 min. Less channel deformation occurred using this method.¹¹¹ Yu *et al.* demonstrated a low temperature and distortion-free bonding method to produce a PMMA microfluidic device using polyvinyl alcohol (PVA) coating and oxygen plasma treatment.¹¹² Likewise, Lin *et al.* considered the same technique using a double-sided adhesive film to produce COC, PC, and PMMA microfluidic devices.¹¹³ All the parameters involved in the non-conformal sealing processes are summarized in Table 3.

3.2.2.5. Limitations. Despite the many advantages with the above-mentioned methods, they still have several limitations. The thermal fusion bonding depends on the T_g of substrates and yields relatively high bond strengths. However, undetermined temperatures and pressures or materials with different T_g result in channel deformation and collapse. Furthermore, in solvent bonding, the formation of bond could be hermetic due to the solvent uniformly spread over the surface of the substrates. However, this technique requires reasonable surface area for proper sealing and demands for adequate ventilation, while the bonding and drying stages are also impor-

tant considerations. Ultrasonic welding process is ideal because it develops stable bonds without introducing any impurities or thermal distortion to the substrates being sealed. However, this method requires lower moisture content in the materials, high fabrication cost, and cannot be used to produce large joints (greater than 250×300 mm). Finally, the bonding assisted by the surface treatment method required the use of high pressure, which could distort the microchannels. Therefore, other feasible technique is still necessary for sealing the thermoplastics and elastomers.

3.3. Methods for sealing PDMS with rigid substrates

3.3.1. Fabrication of channels in PDMS. PDMS has become the most demanding material for the microfluidic community due to its easy availability and simple fabrication. To fabricate microfluidic structures in PDMS, various techniques have been proposed, such as wet and dry etching,¹¹⁴ photolithography,¹¹⁵ laser ablation,¹¹⁶ and soft lithography.¹¹⁷ In almost every academic research laboratory, replica molding is used as a standard fabrication technique.

3.3.2. Bonding methods. In general, one or two silane reagents were used to modify the surface of the PDMS and thermoplastics to produce an irreversible bond between the substrates. The surface chemical bonding of PDMS with rigid materials as well as the resulting bond strengths are discussed below.

3.3.2.1. Surface chemical modification using one silane reagent. The advantage of PDMS is that it can seal to itself or to other substrates without deformation of the channels to make a reversible or irreversible bond. Moreover, a reversible bond is realized simply by van der Waals force, but cannot sustain pressure above 5 psi. Therefore, the surface of PDMS can be readily modified by chemicals such as silane coupling reagents. In this section, we discuss the publications reported

Table 3 Summary of various bonding techniques and bonding parameters used for sealing non-conformal polymers

Method	Materials	Process parameters	Applications	Ref.
Thermal fusion bonding	PC-PC	155 °C, 30 min	Capillary electrophoresis (CE)	85
	PC-PC	128 °C, 0.1 MPa, 30 min	Electrochemical detection	87
	PMMA-PMMA	97 °C, 0.6 MPa, 15 min	CE	88
	PMMA-PMMA	91 °C, 1.4 MPa, 360 s	NA	89
	PMMA-PMMA	165 °C, 0.02 MPa, 30 min	Biological application	90
	PMMA-PS	125 °C, 0.51 MPa	NA	91
Solvent bonding	PMMA-PMMA	Acetonitrile, RT, 15 min	CE	95
		90% ethanol, UV, 1 min	NA	99
		75% acetone, 40 °C, 20 min	Cell culture	100
		Isopropanol (IPA), 80 °C, 30 min, 0.26 MPa	NA	101
		Ethanol, 100 °C, 9 min, 0.024 MPa	Micro-total-analysis system (μ -TAS)	102
		80% IPA : 20% DCM, 70 °C, 5 min	NA	103
Ultrasonic welding	PMMA-PMMA	0.05 W cm ⁻³ intensity	NA	106
	PMMA-PMMA	30 °C, 30 s	NA	107
	COC-COC	400 N, 0.05 MPa	NA	109
Surface modification	PMMA-COC	UV/O ₃ , 110 °C, 10 min, 4.8 MPa	NA	53
	PMMA-PMMA	UV, 45 °C, 35 min	Ion enrichment-depletion	110
	PMMA-PMMA	85 °C, 15 min, 3.44 MPa	Protein separation	111
	PMMA-PMMA	O ₂ plasma, 70 °C	NA	112

Table 4 Various methods for bonding PDMS with thermoplastics/SU-8/metals and bond strengths of the fabricated device

Bonding substrates	Bond strength (kPa)	Bonding conditions	Temperature (°C)	Time	Ref.
PDMS-PDMS	184	O ₂ Plasma treatment followed by surface modification with 1% APTES and GPTMS	RT	1 h	33
PDMS-PC	430	O ₂ Plasma treatment followed by surface modification with 1% APTES	RT	A few minutes	34
PDMS-COC	432				
PDMS-PMMA	385				
PDMS-PS	388				
PDMS-PMMA	510	O ₂ Plasma treatment followed by surface modification with 1% APTES and GPTMS	RT	1 h	35
PDMS-PC	579				
PDMS-PET	579				
PDMS-U-PET	607				
PDMS-PDMS	406	O ₂ Plasma treatment followed by surface modification with 5% APTES	RT	A few minutes	118
PDMS-PMMA	1130				
PDMS-PC	—	Corona discharge treatment followed by surface modification with 5% BTESE	70	24 h	133
PDMS-Polymer membrane	227.8	O ₂ Plasma treatment followed by surface modification with 1% APTES	RT	A few minutes	121
PDMS-PMMA	2500	Corona discharge treatment followed by surface modification with 5% APTES	65	2 h	122
PDMS-Thermoplastic	—	Corona discharge treatment followed by surface modification with 6% TMSPMA	90	Overnight	134
PDMS-Au	296	O ₂ Plasma treatment followed by surface modification with 1% APTES	RT	A few minutes	125
PDMS-Pt	401				
PDMS-Cu	312				
PDMS-Fe	597				
PDMS-Al	200				
PDMS-PP	170				
PDMS-HDPE	130				
PDMS-Teflon	30				
PDMS/SU-8	1500	O ₂ Plasma treatment followed by surface modification with 99% APTES	150	2 h	128
PDMS/SU-8	1400	O ₂ Plasma treatment followed by surface modification with 5% APTES	90	30 min	130
PDMS-PMMA	335.9	Corona discharge treatment followed by surface modification with 2% MPTMS	RT	A few minutes	132
PDMS-PET	476.4				
PDMS-PVC	467.3				
PDMS-PC	511.4				
PDMS-Al	282.2				
PDMS-Cu	236.7				
PDMS-COC	700	O ₂ Plasma treatment followed by surface modification with 5% APTES and GPTMS	80	2 h	136
PDMS-PMMA	305.8	Corona discharge treatment followed by surface modification with 5% APTMS	RT	15 min	138
PDMS-PC	219.7				
PDMS-PET	189				
PDMS-PS	475.7				

since 2009 and summarize relevant characteristics, such as bonding substrates, bond strength, bonding conditions such as bonding temperature, pressure, and time as summarized in Table 4.

Initially, (3-aminopropyl)triethoxysilane (APTES) was used for surface modification of the thermoplastics. For instance, Vlachopoulou *et al.* demonstrated a low cost and low-tempera-

ture process for producing hybrid microfluidic device using 5% APTES heated at 80 °C for 20 min. Later, the PDMS and the functionalized PMMA surfaces were exposed to oxygen plasma and contacted with each other for 1 h with 0.5 kg of pressure to produce a PDMS-PMMA device with the bond strength of 1130 kPa (Fig. 2).¹¹⁸ The bond strength was measured to be incomparably higher than the reported

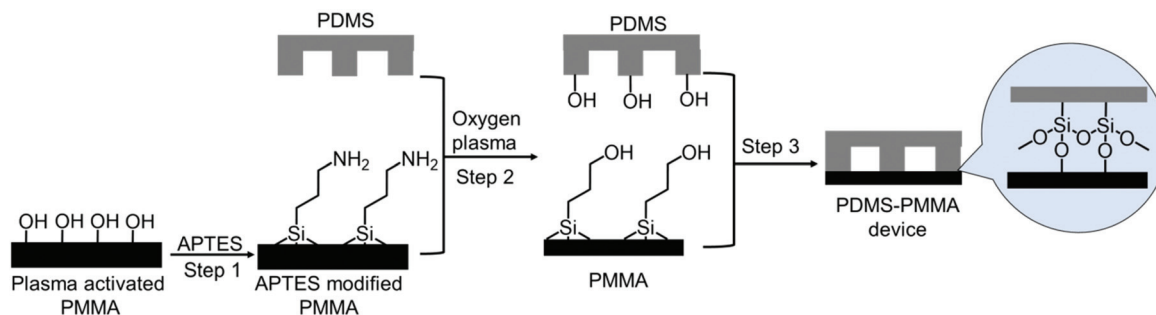


Fig. 2 Fabrication of PDMS–PMMA microfluidic device assisted by coating with aminosilane.

method of 15 kPa,³² and that of the PDMS–PDMS device which was 474 kPa in the bond strength.¹¹⁹ Similarly, Huang *et al.* followed the same technique to fabricate a four-layer structure of PMMA/PDMS–PDMS/PMMA microfluidic device which can sustain at least 1 MPa pressure without leakage or delamination.¹²⁰

Likewise, Aran *et al.* also tracked the above techniques and explored an irreversible bonding of nanoporous polymer membranes made of polycarbonate (PCTE), polyethersulfone (PES), and polyethylene terephthalate (PETE) to PDMS or glass microfluidic structures.¹²¹ The results of this study showed that the bond strength of the device made from APTES-coated membranes remained high (over 227.8 kPa) as compared to other devices made up of PDMS glue (26.5 kPa) and epoxy glue membranes (22.3 kPa). Using another method, Kim *et al.* presented an optimized sealing method for PDMS–PMMA with minor modification of the above methods, *i.e.*, the surface modification took just one minute, and corona discharge treatment was used instead of oxygen plasma to the PDMS and the silane-modified PMMA surfaces. After the corona discharge treatment, two surfaces were brought into conformal contact and placed in an oven at 65 °C for 2 h to produce irreversible seal for PDMS–PMMA.¹²² The tensile bond strength between PMMA and PDMS was 2.5 MPa, and this value was much higher than corresponding values reported in other studies.^{119,123,124}

Sunkara *et al.* further modified the above procedure by changing the concentration of the APTES from 5% to 1%, and irreversible bonding of PDMS–thermoplastics was achieved at RT.³⁴ In addition, the tensile strength of PDMS bonded with PC, COC, PMMA, and PS were shown to be 430, 432, 385, and 388 kPa, respectively. This study also explored how hard materials such as Au, Pt, Cu, Fe, Al, PP, HDPE, and Teflon bonded with PDMS at RT to obtain irreversible bond (Fig. 3).¹²⁵ Furthermore, Hwang *et al.* fabricated a PDMS–PC microfluidic device using the above strategies.¹²⁶

SU-8 is a promising material that can be used to fabricate functional microfluidic devices with high bond strength in place of thermoplastics. Hamdi *et al.* designed a silanization process of the SU-8 microchannels and bonded with PDMS to realize irreversible bond.¹²⁷ In this process, the SU-8 surface was exposed with oxygen plasma, followed by the treatment with 9% methanolic solution of APTES for 30 min at 110 °C. Then, the silanized SU-8 and PDMS were simultaneously

PDMS–Hard materials devices			Characteristic
			1% of APTES solution was utilized for surface modification - PDMS–Pt produced the highest bond strength (401 kPa) - PDMS–Teflon produced the lowest bond strength (36 kPa)
			
			

Fig. 3 Various hard materials functionalized with APTES for the bonding with PDMS. The images are reproduced from ref. 125 with permission from Royal Society of Chemistry, Copyright 2012.

exposed to oxygen plasma and brought into contact for irreversible bonding at 70 °C for 20 min. The bond strength of the hybrid PDMS/SU-8 device was 1200 kPa, and the irreversible bond of the device was confirmed by the manual delamination test (Fig. 4).

Another study used the same substrates for bonding, but different bonding conditions to obtain higher bond strength of the device. In this study, 99% of APTES was used to modify the PDMS surface followed by the reaction between amine group on the PDMS surface and epoxy group on the SU-8 surface to realize irreversible bond at 150 °C for 2 h.¹²⁸ Using this method, the bond strength was measured to be 1500 kPa, which was higher than the corresponding values attained using the previously published method.^{127,129} Zhu *et al.* reduced the bonding temperature and time compared with the above-reported methods by a simple modification. In this method, both plasma-activated PDMS and SU-8 surfaces were immersed in the APTES solution, and the functionalized surfaces were brought into contact at 90 °C for 30 min to produce an irreversible bond with the bond strength of 1400 kPa (Fig. 5).¹³⁰

Apart from APTES, some other chemicals were also involved in fabricating the hybrid microfluidic devices. For instance, Baraket *et al.* designed a new approach for bonding PDMS and thermoplastics using (3-mercaptopropyl) trimethoxysilane (MPTMS) as a silane reagent.¹³¹ At first, the surfaces of thermoplastics including polyimide (PI), polyethylene naphthalate (PEN), and polyethylene terephthalate (PET) were activated

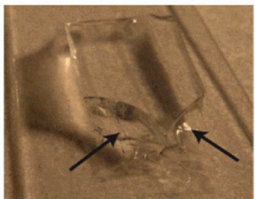
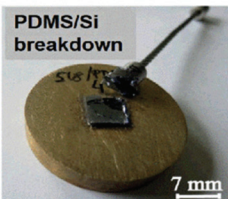
PDMS/SU-8 Devices	Characteristics	Ref
 Delamination Test	 Pull Test	● SU-8 surface was modified with APTES ● Upon peeling, only PDMS covers were torn ● The tensile strength was 1.2 MPa
		127

Fig. 4 Images of delamination and pull tests for PDMS/SU-8 device and the images are reproduced from ref. 127 with permission from IEEE, Copyright 2014.

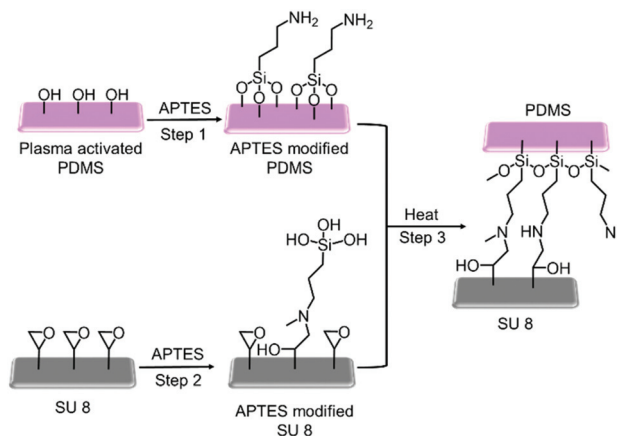
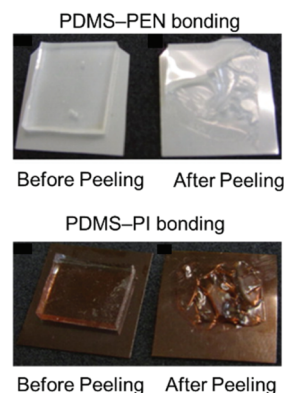


Fig. 5 Simultaneous surface modification using APTES and the reaction between functionalized PDMS and SU-8.

through the 3 M KOH solution followed by immersion with 0.3 M solution of MPTMS at RT. Finally, the oxygen plasma was applied to both surfaces, and the surfaces were contacted to produce an irreversible bond without pressure or high temperature to initiate the bonding. The results of the delamination test confirmed the formation of the high strength bond (Fig. 6). Similarly, Wu *et al.* used same silane reagent (MPTMS) for irreversible bonding of PDMS with non-silicon-based materials including thermoplastics, metals, an alloy, and ceramics at RT.¹³² In this study, the PDMS and MPTMS-modified substrates were treated with corona discharge for 2 min and brought into contact with each other to realize irreversible bonding at RT for 10 min. Furthermore, the bond strength of PDMS with PMMA, PET, PVC, PC, Al, and Cu were measured to be approximately 335.9, 476.4, 467.3, 511.4, 282.2, and 236.7 kPa, respectively, and these results were higher than those obtained using the previously published method (Fig. 7).³⁵

In another report, Lee and Ram has fabricated a PDMS-PC device through the 1,2-bis(triethoxysilyl)ethane (BTESE) silane reagent.¹³³ In this method, after the surface treatment of PC, it was immersed into 5% of BTESE solution and subsequently exposed to corona discharge. Then, it was bonded with corona discharge treated PDMS at 70 °C for 24 h to produce an irreversible bond. Furthermore, 3-(trimethoxysilyl) propyl methacrylate (TMSPMA) is one of the silane reagents used to bond

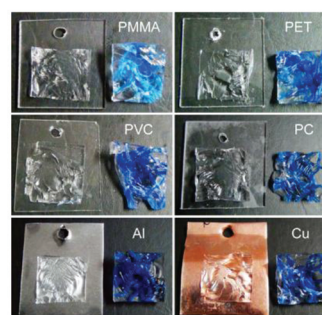
PDMS-thermoplastic devices



- Surface modification with 0.3M MPTMS solution
- The ragged surface was formed when PDMS was peeled off the thermoplastics

Fig. 6 Images showing the results of delamination test for PDMS-thermoplastic devices. The images are reproduced from ref. 131 with permission from Elsevier, Copyright 2013.

PDMS-non-silicon substrates devices



- 2% aqueous solution of MPTMS was utilized for surface modification
- High bond strength for PDMS-PC (511.4 kPa)
- Low bond strength for PDMS-Cu (236.7 kPa)
- Strong bond formation was confirmed by conducting leakage test
- The method was stably applicable for large area bonding

Fig. 7 Tensile strength for PDMS-non-silicon substrate devices produced via MPTMS surface modification. The images are reproduced from ref. 132 with permission from Royal Society of Chemistry, Copyright 2015.

thermoplastics such as COC and PMMA to PDMS.¹³⁴ In this technique, 6% of TMSPMA was used to modify the corona discharge treated thermoplastics, and both surfaces (PDMS and thermoplastic) were exposed to corona discharge, contacted

with each other, and then kept in an oven overnight at 90 °C to realize irreversible seal between PDMS and thermoplastics.

3.3.2.2. Surface chemical modification using two silane reagents. Lee and Chung has first introduced two silane reagents such as APTES and 3-glycidypropyltrimethoxysilane (GPTMS) for bonding two PDMS substrates in order to reduce bonding temperature and time, since it was reported that amine and epoxy functionalities react to form amine-epoxy bond at 25 °C.³³ In their experiment, two PDMS substrates—PDMS replica and a flat PDMS—were exposed to oxygen plasma for 1 min, followed by immersion into the 1% aqueous solution of APTES and GPTMS for 20 min which was brought into contact for 1 h at RT to produce a PDMS–PDMS microfluidic device with the bond strength of 184 kPa. This was equal to the results obtained using the conventional oxygen plasma method.¹¹⁸ Similarly, Tang and Lee has demonstrated a simple and robust PDMS–thermoplastic bonding by adopting the above method (Fig. 8).³⁵ In addition, when compressed air was introduced into the bonded microfluidic devices, PDMS microfluidic chips realized by bonding with PMMA, PC, PET, and urethane-coated PET (U-PET) endured pressures as high as 74, 84, 84, and 88 psi, respectively, which were relatively equivalent to or even higher than the reported PDMS–glass microfluidic devices.¹³⁵

Likewise, by adopting the previously reported procedure, with minor modifications, Cortese *et al.* bonded COC to a thin PDMS membrane.¹³⁶ In this study, COC and PDMS membrane surfaces were modified using 5% of APTES and GPTMS for 1 h at 50 °C, instead of using 1% of APTES and GPTMS. Then, the two surfaces were brought into conformal contact and were maintained at 80 °C for 2 h to ensure permanent bond. Delamination and leak did not take place when approximately 700 kPa of pressure was applied into the microchannel. Similarly, Ogilvie *et al.* followed the same procedure, replacing only the PDMS with Viton® membranes.¹³⁷ In this procedure, amine-terminated thermoplastic and epoxy-terminated Viton® membrane were clamped and pressed under 800 kPa at 80 °C

for 12 h to form an irreversible bond. Furthermore, the bond strength was sufficient to manage the fluid pressure of 310 kPa for COC–Viton® and 400 kPa for PMMA–Viton®.

More interestingly, Lee *et al.* made an important contribution to fabricate hybrid PDMS–thermoplastic microdevices adopting different silane coupling reagents. This study introduced a new chemical, namely, monoglycidyl ether terminated, low-molecular-weight PDMS, in place of GPTMS for bonding PDMS–thermoplastics *via* C–N bond formation by the amine-epoxy reaction.^{138,139} After the treatment with corona discharge of the thermoplastic, it was treated with 5% aqueous solution of APTES at 80 °C for 20 min. Then, it was reacted with monoglycidyl ether terminated, low-molecular-weight PDMS at 80 °C for 4 h to produce chemically robust C–N bond (Fig. 9). Finally, both the PDMS monolayer-coated thermoplastic and flat PDMS were plasma oxidized and brought into contact at 25 °C for 15 min under 0.1 MPa to form an irreversible bond. The average bond strength of PDMS bonded with PMMA, PC, PET, and PS were found to be 305.8, 219.7, 189, and 475.7 kPa, respectively.

Similarly, Wu and Lee has again attempted to replace the silane reagents such as APTES and GPTMS with a new chemical, namely, poly[dimethylsiloxane-*co*-(3-aminopropyl)methylsiloxane] (amine-PDMS linker), a chemical containing a PDMS backbone with amine functional group, for the irreversible

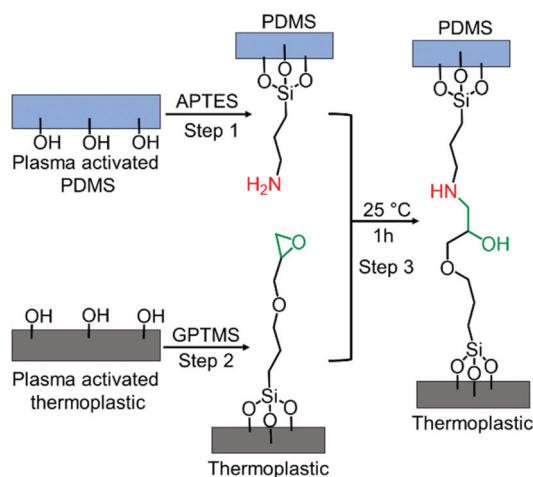


Fig. 8 Bonding between PDMS and thermoplastics using APTES and GPTMS reagents.

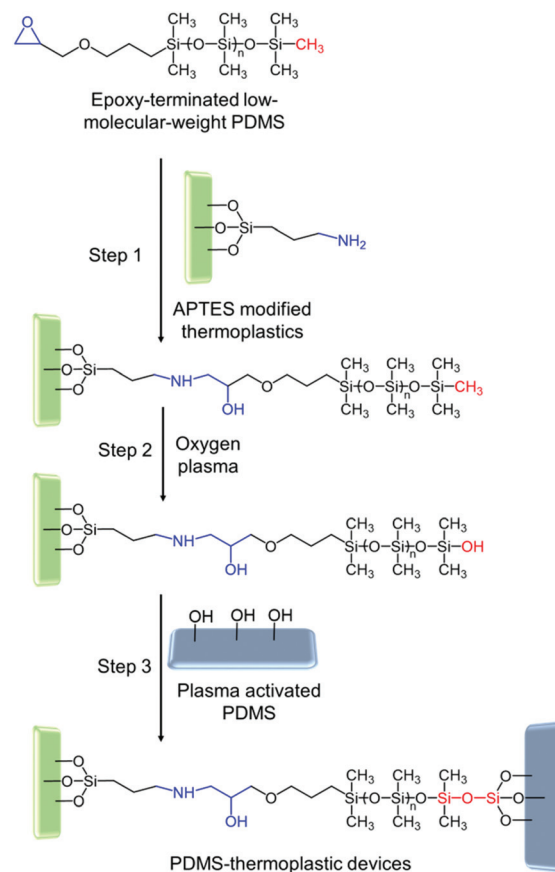


Fig. 9 Scheme for PDMS–thermoplastic devices by surface modification using epoxy-terminated PDMS.

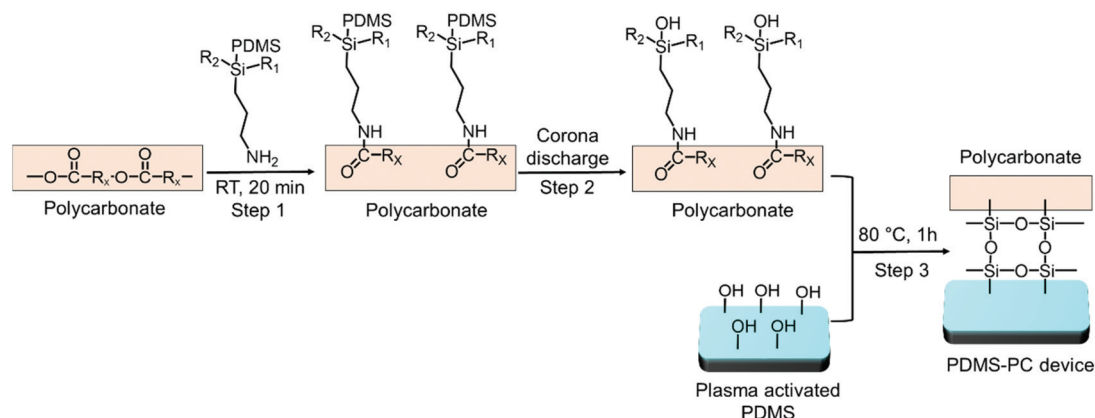


Fig. 10 Coating of amine-PDMS linker on the surface of polycarbonate to realize PDMS-PC microfluidic device.

bonding of PDMS to various plastic substrates at RT.¹⁴⁰ In this method, thermoplastics containing carbonate backbone were used because amine functionality in the amine-PDMS linker is known to undergo aminolysis of the thermoplastic surface at RT without any further treatment.^{141,142} After sonication for 1 min to remove excess amine-PDMS linker, a flat PDMS and amine-PDMS linker-coated thermoplastics were exposed to corona discharge for 1 min and were placed in conformal contact with each other to realize permanent seal at $80\text{ }^\circ\text{C}$ for 1 h (Fig. 10). The bond strengths of PC, PET, and PVC with PDMS were calculated to be approximately 428.5 ± 17.9 , 361.7 ± 31.2 , and 430 ± 14.9 kPa, respectively, and these values were equivalent to or higher than those obtained using the previously reported methods.^{33–35} Similarly, Nguyen *et al.* followed the same aminolysis mechanism for bonding pristine PC with aminosilane-terminated PDMS. The aminosilane-terminated PDMS was brought into intimate contact with a pristine PC so they could simply bond *via* aminolysis of PC initiated by the amine functional group of the aminosilane-terminated PDMS at RT. This method is particularly useful when immobilizing cells or biomolecules in a spatially controlled manner inside a microchannel or encapsulating heat fragile objects such as optical fiber before sealing the microdevice. The bond strength of the fabricated PDMS-PC device was measured to be 409 ± 6.6 kPa which was used to perform a chamber-type polymerase chain reaction (PCR) to detect foodborne pathogens.¹⁴³

4. Conclusion

This review explored numerous bonding strategies to construct microfluidic device using various materials, with particular emphasis on the surface chemical modification to assist in the bonding of elastomer, mainly PDMS, with thermoplastics and metals, to enable sealing at room temperature under atmospheric pressure which eliminated the use of bulky and expensive tools such as a heater or press machines so as to make this technique readily available to any laboratory in need of utilizing microfluidic devices for the experiment. To fabricate high performance microfluidic devices, bonding substrates,

bonding conditions such as temperature, pressure, and time, resulting bond strength, possibility for large area bonding, and many other issues need to be considered, and the surface chemical bonding method almost satisfied all the key parameters which were mentioned above, realizing hybrid micro-devices at room temperature under atmospheric pressure within a few minutes mainly assisted by the use of chemicals such as silane coupling reagents. Considering the immense advantages such as maintaining the integrity of microchannels offered by both room temperature and atmospheric pressure conditions, combined with the formation of the stable covalent bond which could endure at high temperature and pressure, the surface chemical bonding technique should be more extensively used in future studies. Furthermore, large area bonding was also realized using chemical bonding techniques, which enhances its potential for commercialization. Nevertheless, there still exists some shortcomings to be resolved such as large scale production and compatibility with chemical reactions involving organic solvents. If all these are well resolved, we strongly believe that the surface chemical bonding technique could be applied readily in any laboratory, and could be settled as a mainstream fabrication and sealing technique for mass production of microfluidic devices.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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