Forming the Microchannel Geometry

Subjects: Engineering, Manufacturing

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Various fields within biomedical engineering have been afforded rapid scientific advancement through the incorporation of microfluidics. Microfluidics is the study of fluid flow in geometries with one of the channel dimensions being of the micrometer scale. These geometries are built up into circuits known as microfluidic chips.

Keywords: microfluidics ; thermoplastics ; fabrication strategies

1. Hot Embossing

Hot embossing is a common technique for the mass production of thermoplastic polymers with medium costs [1][2][3][4][5][6][7]. In hot embossing, the polymer plate is heated above the glass transition temperature (Tg) while it is pressed against a master mold with channel protrusions by a hydraulic press to form the microfluidic arrays as cavities in the polymer. The thermoplastic polymer plates used in hot embossing could be fabricated by injection molding [8][9]. Before performing the hot embossing process, the polymer plate may be annealed to reduce residual stress [8]. Depending on the polymer type, thickness, polymer chain orientation, and the experimental design, the applied pressure and temperature vary. After the process, which takes a few minutes (e.g., 2–20 min), the pressure is usually maintained as the samples cools down to enhance the uniformity [4][10].

Hot embossing was done at 150 °C on a COC pellet for 6 min under 1.38 MPa, followed by maintaining the polymer for 10 min at 25 °C under the same pressure [10]. Additionally, polycarbonate (PC) microchannels were prepared via compressing PC plates on a photolithographic patterned silicon mold at 155 °C with 1.2 MPa for 2 min followed by 5 min at 50 °C, while the pressure was kept constant [1]. Young et al. hot embossed polystyrene (PS) substrates against an epoxy mold at 125 °C under the 900 kgf pressure for 15 min [5]. Cyclic Olefin polymer (COP)/cyclic olefin copolymer (COC) have shown superior performance compared to poly(methyl methacrylate) (PMMA) chips fabricated via hot embossing, with higher signal to noise ratios and higher electrophoresis efficiencies due to their low impurity levels and high glass transition temperatures [11]. The embossing reference temperature (143 °C) for COC/COP microchannels is determined by the viscoelastic property of these polymers, while other processing parameters, such as the temperature, time, and pressure in the cooling and demolding stages, are determined by the Taguchi method. A COP microfluidic channel is said to have a high repeatability and low substrate deformation when it exhibits the following optimized parameters: reference temperature 143 °C, holding time 2 min, pressure 1.6 MPa, and demolding temperature 80 °C [12].

Hot embossing is also a popular method to create microchannels out of thermoplastic elastomers (TPEs). The produced microchannels are transparent, flexible, and biocompatible [13][14][15]. Schneider et al. used this technique to make PC/TPE-hybrid microfluidic channels using epoxy-based master molds [15]. Hot embossing can be integrated with roll-to-roll printing, where a rotating embossing cylinder is used to transfer the microchannel features of the cylinder into a heated polymer web continuously fed into the system [16]. In order to create the embossing cylinder with the desired features, an embossing shim (thin strip of material on the cylinder) can be fabricated from a flexible steel using wet-etching and then laser welded to the cylindrical sleeve [16]. As roll-to-roll hot embossing continues heating and forming the substrate, it is considered a faster approach compared to normal hot embossing or micro-injection molding techniques. Runge et al. presented a different type of hot embossing process, where a PC thermoplastic polymer was pressed against a master mold via a tool capable of generating ultrasonic vibrations (sonotrode) [17]. The induced friction as a result of the vibrations could rapidly increase the temperature of the substrate above the glass transition temperature and form the desired patterns on the sheet. The process could be completed in a few seconds, which enables rapid replicating of thermoplastic microfluidics. However, the size of the channel that is possible to form by this method is typically limited to 50 µm to 1 mm in depth and 100 µm to 3 mm in width.

2. Injection Molding

Injection molding is another method frequently used to create microchannels in thermoplastics [9][18][19][20]. In this process, the thermoplastic polymer granules are melted (plasticization step) and injected into the mold cavity. The molten polymer is then solidified as the temperature decreases below the glass transition temperature (cooling stage) and finally ejected from the mold. The molding process is done under constant pressure to compensate for the shrinkage of the polymer during solidification. The process cycle takes seconds to a few minutes [19]. In addition to polymeric material properties, several process parameters, such as melt temperature and mold temperature, speed of filling and packing time as well as packing and holding pressures, attribute to the efficiency of the process and quality of the final product [21]. Ogorodnyk et al. have conducted a comprehensive review on the implementation of artificial intelligence (AI) methods for the monitoring and controlling of the parameters involved in injection molding [22]. The cooling stage is the most time-consuming part of the injection molding. In order to accelerate the process, rapid heating and cooling technologies by means of conformal cooling or variotherm system have been introduced. Conformal cooling could be conducted via accommodating cooling channels in the mold and conforming them to the shape of the mold cavity. The cooling channels can be made in different designs, such as spiral conformal cooling channels [23], milled grooved square shape conformal cooling channels [24], and longitudinal conformal cooling channels [25]. Conformal cooling significantly reduces the cooling time in a more uniform and consistent way by increasing the heat transfer efficiency, thereby enhancing the quality of the formed thermoplastic polymer. The channels in conformal cooling could also be used for heating the injected thermoplastic in order to prevent it from early solidification during the injection process as premature solidification can lead to defect formation in the product. In variotherm injection molding, the mold temperature is dynamically controlled according to each stage of the process. Before the injection, the temperature is raised to the glass transition temperature of the thermoplastic polymer. Then, the temperature is increased above the glass transition and kept constant during the mold filling step. Afterwards, the mold is rapidly cooled for the solidification of the polymer and the ejection step. Controlling the temperature could be performed by electromagnetic induction heating, which can heat the mold from 110 °C to 200 °C in only 4 s [26]. By using a proper coolant, the cooling time also takes only 20 s to reach 110 °C again [26]. Another way to heat the mold is to use steam at a temperature of 180 °C, which can increase the temperature in injection molding from 30 °C to 140 °C in 20 s [27]. Water can be used in this approach to cool the mold and solidify the injected polymer. CO_2 lasers have also been used to heat the injected resin [28].

Ma et al. have thoroughly investigated the injection molding of PMMA-based microfluidic devices using a horizontal single screw injection molding machine capable of performing each injection cycle in 45 s [29]. They set the injection pressure at 120 MPa and the speed ranged between 200 mm/s to 400 mm/s. The injection was performed at 60 °C using an oil mold temperature controller. In another study, Kim et al. applied 5.5 MPa injection pressure and clamping force of 130 tons to create PS microfluidic channels at 220 °C in 15 s and used the device for single cell analysis [30]. Using the same injection molding parameters, Ko et al. fabricated an open circular microfluidic chip made of PS for ocular angiogenesis applications [31]. Injection molding was also adopted in Viehrig et al.'s work to form nanocones in COC through a nickel master mold [32]. The device was employed for SERS sensing applications.

In general, hot embossing and injection molding are more appropriate for medium-cost mass production through replication methods and can be implemented for the manufacturing of complex channel designs. Moreover, the quality of surface finish in these methods is superior compared to other methods, such as laser machining, micro-milling, and 3D printing. Injection molding is a very rapid method allowing for large-volume production. Hot embossing, in comparison, has an average production rate, but it requires less expensive tools and infrastructure. The primary disadvantage of injection molding pertains to limitations when fabricating microchannels with large footprints, whereas in hot embossing, large area machining is possible. It is worth mentioning that the polarity of the thermoplastic polymers affects their meltability. High polar polymers are very difficult to melt in their pure form due to their strong interchain forces [33]. Moreover, polar thermoplastics are not quite permeable to oxygen and carbon dioxide, which could be problematic in cell culture applications. Polar thermoplastics also have poor water barrier properties, which can lead to changes in local concentrations when implemented within applications that use water-based buffers and liquids. A comparison between the polarities of different thermoplastic polymers can be found elsewhere [34].

3. Master Mold Fabrication

The master molds used for the fabrication of thermoplastic polymers in both hot embossing and injection molding are usually fabricated by photolithography [1][2][8][35]. Nevertheless, several other fabrication methods, such as e-beam writing, electroforming, micro-milling, and electro discharge machining, laser machining, ion machining, additive manufacturing, and ultrasonic machining, are applicable for master mold production [19], as long as the master mold can withstand the high pressures and temperatures used in the hot embossing or micro-injection techniques. High-precision nickel molds [3]

[4][9][36], micro-milled aluminum [30][31][32], and Zr-based bulk metallic glass mold [20] are other master molds used in literature. For instance, a negative master mold was produced in Müller et al.'s work via electroplating Ni on a 3D printed master mold [36]. The negative master mold was then used for creating COC microchannels through injection molding. Hupert et al. used a high-precision micro-milling machine, which had positional and repetition accuracy of ± 1 µm, a laser measuring system and an optical microscope to create microstructures on a brass plate to be employed as a mold for the hot embossing of PMMA substrates [37]. In another interesting study, Perrone et al. used micro-second pulsed CO_2 laser-based ablation to create microstructures on quartz [38]. The fabricated mold was then utilized to from hundreds of micron-sized pillars on COC substrates through hot embossing method. The final microfluidic device showed great potentialities in 3D cell culturing and organs-on-chip applications.

Micro-milling of brass templates has also been performed in other studies to create master molds for hot embossing microchannels in PMMA, PC, and COC substrates [39][40]. polydimethylsiloxane (PDMS) has also been utilized as a master mold for the fabrication of thermoplastic polymers [10]. In Chantiwas et al.'s study, PDMS master molds were prepared by casting PDMS at a base: curing agent ratio of 10:1 (*w:w*) in PMMA replicated micro/nano channels [39]. After curing the PDMS and peeling it off, it was used to hot emboss other PMMA substrates under a pressure of 0.16 MPa at 155 °C for 30 min. Schneider et al. generated a negative PDMS mold by casting PDMS on an SU-8 coated silicon wafer. They used this negative PDMS mold to produce an epoxy-based master mold for creating microfluidic channels made of TPE/PC, using hot embossing approach [15].

4. Laser Ablation

Another technique used for fabrication of the thermoplastic polymers with microfluidic channel cavities is laser ablation, which is applicable to many polymers, such as PC, COC/COP, PMMA, PS, nitrocellulose, polyethylene terephthalate (PET), polyester terephthalate (PETE), and Teflon [41][42][43][44][45][46][47][48][49][50]. In this method, short laser pulses in the ultraviolet (UV) region (~200 nm wavelength) breaks the polymer chains. The decomposed polymer fragments, such as CO_2 and CO gas, and polymer molecules are subsequently ejected due to the induced shock waves leaving photo-ablated cavities [44]. Patterning the microchannel arrays can be conducted by using photo masks in the process resulting in straight vertical walls without any significant thermal damage. It should be noted that laser ablation in the UV wavelength cannot be used for thermoplastic polymers, such as COC/COP due to their low UV absorption. Thus, infrared lasers, such as CO_2 or Nd:YAG laser systems, should be adopted for microchannel formation. Namely, Liu et al. fabricated a COP-based microfluidic channel via CO_2 laser ablation using pulse mode at a maximum frequency of 1 kHz, whereas a Gaussian-like profile was left on the surface of the COP plate as the COP melted, decomposed, and evaporated. They concluded that the main parameters affecting the profile of the microchannel included the power and scan speed of the laser, as well as the focusing accuracy of the laser and the mechanical transmission system [48]. CO_2 laser ablation was also adopted to pattern PC and polylactic acid (PLA) sheets with the desired micro-features [41][51] and to create microchannel arrays in PET foils [52]. Laser ablation is also possible via desktop CO_2-free laser cutters to create the sheets and membranes with the desired geometries [50]. Commercially available laser systems are flexible approaches for rapid redesign of channel geometries and are usually cheaper than some other techniques, such as injection molding, which requires metal molds or photolithography—a process that needs to be conducted in a cleanroom. The main drawbacks of laser ablation technique are the poor quality of the surface finish and its incapability for the fabrication of complex microchannel designs [53]. Further, the cut profile in conventional laser cutters is only limited to Gaussian-shaped profile or through cuts [54]. Formation of bulge along the scan route is another common problem associated with laser cutting technique [55]. Chai et al. showed that high thermal resistant thermoplastic polymers, such as polyformaldehyde (POM), can be CO_2 laser cut without formation of bulges and carbide residue, and the channel depth and width are easily adjustable by changing the scan speed and laser energy [56]. Covering PMMA substrates by photoresist or PDMS is another way to tackle the bulge formation [57].

5. Additive Manufacturing

Nowadays, additive manufacturing of thermoplastic polymers has produced great interest in microfluidics due to its short fabrication cycle time. However, the resolution of 3D printed microchannels, mechanical properties, as well as the optical quality of the surface finish is not as good as the other techniques [58]. Additive manufacturing is a 3D digital manufacturing process that involves the fabrication of small batches of 3D parts layer-by-layer under accurate digital control, specifically used for applications that demand high-throughput production. Commonly used 3D printing methods include two photon polymerization, fused deposition modeling (FDM), selective selective laser sintering, stereolithography, laminated object manufacturing, and inkjet 3D printing [59]. A superior advantage of 3D printing is its ability to form three-dimensional structures with intricate and complex features with fewer space requirements in a single step from a digital model [58][60]. For 3D printing of thermoplastic polymers the most commonly used extrusion-based methods include FDM and inkjet printing, which employ materials, such as acrylonitrile butadiene styrene (ABS), polypropylene, polyamide, PLA, COC, PET, PS, and acrylate-based polymers [58][60][61][62][63][64][65][66][67][68][69]. Such methods offer several advantages, such as simplicity, low cost, less waste, usually high speed, and elimination of the need for bonding steps in some cases. FDM involves the extrusion of a heated thermoplastic material from a motor-driven nozzle head followed immediately by spontaneous cooling to harden the material. Thermoplastic filaments are the main printing material used in FDM, however by modifying the extruding nozzle other materials, such as powder or liquid thermoplastics, can also be used. FDM provides the most inexpensive and highly biocompatible productions due to a wide variety of cheap and biocompatible thermoplastics [60][62][63]. Despite its popularity in recent years, it still exhibits limitations when used in microfluidics, such as lack of structural integrity between the layers and weak bonding properties, since the adjacent layers are not well fused as the extruded material immediately hardens [59]. Recent efforts aimed to improve the intra-layer bonding strength of printed objects involve gamma-irradiation post printing [70], as well as employing thermally reversible Diels-Alder reaction to form covalent interactions upon cooling [60]. McAlpine's group successfully fabricated a multi-scale biomimetic nervous-system-on-a-chip device to study viral infection in the nervous system. Using micro-extrusion FDM printing strategies, they created microchannels and compartmented chambers for the co-culture of neurons, glia, and epithelial cells using a custom FDM printer [71]. Dolomite microfluidics recently developed the first FDM printer to create completely sealed 3D microfluidic devices. Using COC, the printer creates leak-free, closed and impermeable microchannels [61].

Typically, additive manufacturing as well as micro-milling and laser ablation are more suitable for fast prototyping of thermoplastic microfluidics. Today, extensive research is being performed to advance the various 3D printing methods of thermoplastic-based microfluidics as an alternative for conventional manufacturing methods. Thus, recent works are mainly focused on the advancement of resolution, precision, optical characteristics, and more biocompatible structures [61][62]. For instance, exploiting the conductive properties of polyionic thermoplastic-elastomers and advancing the inks used in inkjet 3D printing holds great potential in developing more advanced and high-resolution microfluidics. In the near future, people anticipate the use of robots to automatically integrate electrodes, sensors, and actuators during printing of microfluidics, evolving the 2D microfluidic chips to 3D cubes [61][63]. Additive manufacturing of thermoplastic polymers is deeply discussed elsewhere [59][72].

6. Other Methods

Milling [73][74][75][76][77][78] and UV curing (specially for polyethylene glycol (PEG)) [79][80][81][82] are other methods to form the microchannels in thermoplastic polymers. Micro-milling of thermoplastic polymers can be incorporated for the fabrication of complex microchannel profiles with small or large surface areas. The production rate of this process is quite rapid, and it allows for instant changes in the channel design in the production line. Moreover, unlike laser ablation, it can create microchannels with nearly rectangular cross-sections. Nevertheless, the quality of the surface finish is not good in this process. In order to decrease the surface roughness and regain transparency after milling COC substrates, Bruijns et al. exposed the COC substrates to cyclohexane vapor at 60 °C for 1 min [77]. Micro-milling of PMMA substrates was demonstrated in a study done by Tomecka et al. [83]. They used a 500 µm and a 100 µm milling drums rotated at a speed of 12,000 rpm to create convex structures and oval-shape holes inside the convex structures, respectively. UV curing of low molecular weight polyethylene glycol (PEG) monomers, such as PEG dimethacrylate and PEG diacrylate (PEG-DA) on a silicon mold with the microchannels arrays or pillars, can be performed to fabricate PEG microchannels and porous PEG membranes, respectively [81]. During casting, a PET layer modified with urethane groups could be placed on top as the supporting layer to adhere to the acrylate-containing PEG monomers. As the supporting layer, it is also possible to use glass slides treated with phosphoric acrylate or acrylic acid dissolved in propylene glycol monomethyl ether acetate to bind to PEG [81]. In another study, Liu et al. first made an enclosed mold comprising a bottom silicon layer with the channel's array, middle PDMS spacers, and a top glass slide [79]. Afterwards, PEG-functionalized monomer solution containing 85% PEG-DA, 12% poly(ethylene glycol) methyl ether methacrylate (PEG-MEMA), 3% methyl methacrylate, and 2,2′-dimethoxy-2-phenylacetophenone (DMPA) was injected onto the mold and cured for 16 s under UV. Tian et al. also UV cured PEG-DA on a PDMS mold using 1% photoinitiator Irgacure 2959 to form the microfluidic design [82]. UV lithography has also been used to create micro-geometries in PMMA substrates [84][85]. This process involves UV exposure of the PMMA substrate with a photoresist through a mask and development of the photoresist, coating a thick layer of X-ray absorber to the exposed areas to create an X-ray mask, emitting X-ray to form the desired channels, and finally removing the X-ray mask form the substrate.

Chandrasekaran et al. presented a new thermal scribing method to rapidly prototype thermoplastic microfluidic devices [86]. In this technique, a heating pen was incorporated into a commercially available craft cutter machine. The induced heat in the pen could locally raise the temperature of the thermoplastic polymer above the glass transition temperature and precisely pattern the layer with the desired geometry.

Another interesting way to fabricate microfluidic features is via the use of dry films, which were originally developed for printed circuit boards [87][88][89][90]. This technique is usually compared with photolithography—used for fabrication of SU-8 layers, or soft lithography, which is used to prepare molds for casting polymers, such as PDMS. While photolithography is an expensive method that needs cleanroom facilities and expert technicians, the fabrication of microchannels via dry films is a simple cleanroom-free approach that can provide comparable resolution and precision to SU-8 photolithography. Dry films resists (DFR) in different series, such as Ordyl, SUEX, and ADEX, TMMF S as well as SU-8 based DFR are commercially available in different thicknesses. DFRs can be laminated on a variety of different thermoplastic substrates or other types of materials via a simple office laminator. Subsequently, the layer is exposed to UV light through a photomask with the desired features and baked on a hotplate for a short period of time. Afterwards, the layer is immersed in a developer solution to form the cavities. The process of lamination and UV treatment can be performed multiple times to acquire microchannels with different heights or multiple layers (3D microfluidics). The microchannels can become hydrophilic through plasma treatment or polyvinyl alcohol if needed [90]. DFRs have also been utilized as a sealing layer in microfluidics made by injection molding. Moreover, researchers have used DFRs in fabrication of molds for hot embossing and PDMS casting processes [91][92][93]. The most common techniques for forming microfluidic channels are summarized in **Table 1**.

Table 1. Common approaches for forming microchannel.

Method	Experimental Procedure	Effective Parameters	Advantages	Disadvantages	Examples
Hot embossing	• Heating polymer plates above Tg • Pressing against a master mold • Cooling down • Detachment of the formed channels	• Heating and cooling temperatures • Pressure and time of embossing process	✓ High replication accuracy ✓ Capability for mass production especially by integration with roll-to-roll printing ✓ Good surface finish quality ✓ Allows for fabrication of complex microchannel designs ✓ Medium cost	× Average production rate × Requires a master mold × Difficulties in forming channels with high aspect ratios × Possibility of breakage during the detachment step	**PMMA** [6] [16][37][39][40] **COP/COC** [3][4][6][8][10] [11][12][20][38] [39][40] **PC** [1][2][17] [39][40] **PS** [5] **TPEs** [13] [14][15]
Injection molding	• Melting polymer granules • Injection into the mold cavity • Cooling down • Ejection	• Melt temperature and mold temperature • Heating and cooling rate • Filling rate • Packing time and pressure	✓ A rapid process especially by integration of rapid heating and cooling systems, such as conformal cooling and variotherm systems ✓ Tight tolerances and High reproducibility	× Requires expensive tools × Incapable of producing channels with large footprints × Requires a master mold	**PMMA** [29] **PC** [9] **COC** [20][32] [36] **PS** [30][31]

Method	Experimental Procedure	Effective Parameters	Advantages	Disadvantages	Examples
Laser ablation	• Decomposing polymer chains by irradiation of laser through a photo mask • Ejection of the polymer fragments due to the induced shock waves • Cooling down	• Laser power, wavelength and frequency • Scanning speed	✓ A relatively low-cost technique ✓ A rapid process ✓ Flexibility in on-the-fly modification of the design	✕ Poor surface finish quality ✕ Incapable of fabrication of complex microchannel designs ✕ Causes bulge formation ✕ Creates Gaussian-shaped cut profile	**PMMA** [42][43][47][49][50][53][54][55][57] **PC** [41][44] **PS** [44] **PET** [44][45][46][52][94] **PETE** [50] **COP** [48][49] **PLA** [51] **POM** [56]
Micro milling	• Modeling the channel design • Mounting the substrate on the machine and conduct the milling	• Milling speed • Spinning speed of milling drum • Teeth location on milling drum	✓ Allows for fabrication of complex microchannel designs ✓ Rapid production rate ✓ Flexibility in on-the-fly modification of the design	✕ Poor surface finish quality ✕ Poor transparency ✕ High precision and surface smoothness make the process expensive	**PMMA** [73][76][78][83] **PC** [74] **COC** [75][77]
UV-curing	• Injection of polymeric solution into/onto a mold • Irradiation of UV for curing	• Layer thickness • UV exposure time and intensity	✓ Very high resolution ✓ Provides non-biofouling properties when PEG is used	✕ Only applicable to few polymers ✕ Requires master molds or photo masks ✕ A challenging approach for mass production	**PEG-based** [79][81][82] **PMMA** [84][85]
Thermal scribing	• Modeling a CAD design • Inducing channel geometry by a heating pen installed on a craft cutter machine	• Heating temperature • Cutting speed • Proximity of the cutting pen to the plastic	✓ A rapid technique ✓ Inexpensive method ✓ Simplicity of the process	✕ A time-consuming process ✕ Suited for low volume prototyping	**PS** [86]

Method	Experimental Procedure	Effective Parameters	Advantages	Disadvantages	Examples
3D printing	• Preparing a CAD model of the design • Loading the design into slicing software • Printing the design	• Physical and chemical properties of the resin • Printer resolution	✓ A low-cost method ✓ Relatively fast technique for small footprints ✓ Capability for fabricating complex channel designs ✓ Flexibility in quick modification of the design	✕ Poor surface finish quality and optical transparency ✕ Low resolution ✕ Time consuming process for large footprints	**ABS** [64][67][68][69] **PLA** [65][66][68][70] **COC** [61] **Acrylate-based** [70]
Dry films	• Lamination of dry film resists on a thermoplastic substrate • UV exposure through a photomask • Baking on a hotplate • Submerging in a developer solution	• Thickness of the laminated film • UV exposure time and intensity • Baking temperature and time • Developer type and immersion duration	✓ Unlike photolithography, it does not require cleanroom facilities	✕ Requires a photomask ✕ Multiple process cycles should be conducted to form channels with different heights	**ADEX** [87] **SUEX** [87][88][89] **Ordyl** [90]

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