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## Overview of Materials for Microfluidic Applications

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### Abstract

For each material dedicated to microfluidic applications, inherent microfabrication and specific physico-chemical properties are key concerns and play a dominating role in further microfluidic operability. From the first generation of inorganic glass, silicon and ceramics microfluidic devices materials, to diversely competitive polymers alternatives such as soft and rigid thermoset and thermoplastics materials, to finally various paper, biodegradable and hydrogel materials; this chapter will review their advantages and drawbacks regarding their microfabrication perspectives at both research and industrial scale. The chapter will also address, the evolution of the materials used for fabricating microfluidic chips, and will discuss the application-oriented pros and cons regarding especially their critical strategies and properties for devices assembly and biocompatibility, as well their potential for downstream biochemical surface modification are presented.

**Keywords:** microfabrication, prototyping, manufacturing, thermoplastics, thermoplastics elastomers, assembly, bonding

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## 1. Introduction

Following Pasteur microbiology and Curie radiotherapy, the next coming and significant medical revolution is geared toward the foreseen convergence and integration of the following innovative science and technology components for the emergence of a new predictive, personalized, and preemptive medicine and practice. Bioengineering, microbiology, micro-

fluidics, optics, and electrochemistry are today the most significant key enabler disciplines. Their complementary features lead to complex systems and democratization and wide public access to personalized and new medical products that will promote both wealth and innovation at the same time, as the IT industry did in the last decades. This technological trend is of tremendous impacts in both sociological and economical applications. For example, the needs of *in situ* personal monitoring are crucial for the comfort and the health surveillance for our specific aging modern society, and it has become a major concern for the health care system. It offers additional opportunities to lower the hospital workloads and expense. It also promotes enhanced therapy efficiency through real-time and accurate monitoring for proper therapy delivery. The advent of rapid molecular diagnostic systems shortening pathogenic genomic identification down to 1–2 h in an integrated manner, beyond the standard cellular culture identification that may extend from several days up to few weeks is one of the most promising paths for decentralized and personalized medicine. In addition, it is also a powerful asset to address major problems in bacterial antibiotic resistance. Beyond human health, rapid molecular diagnostic approaches deserve multiple segments from water quality control to veterinary and agronomy fields for widely accessible, deployable, and low-cost analytical systems. The others aspects of the emergence of microfluidic polymer systems are to act as template for dedicated and addressable microenvironments, thus promoting the organogenesis of organs reconstruction and substitution and sustaining the development of novel drugs that are cost effective.

Moreover, the microfluidic science and applications are by essence multidisciplinary. For a targeted application, a seamless and holistic vision is of tremendous importance. In this chapter, we aim to provide an overview of materials used for microfluidic applications. Their selection, evaluation, and integration at both prototyping scale and toward mass production are discussed. Due to the fact that some materials and strategy might be suited for specific goals yet not fit for others, the specific drawbacks and advantages regarding their status and potentials toward a path to products are analyzed.

## 2. Materials for microfluidic applications

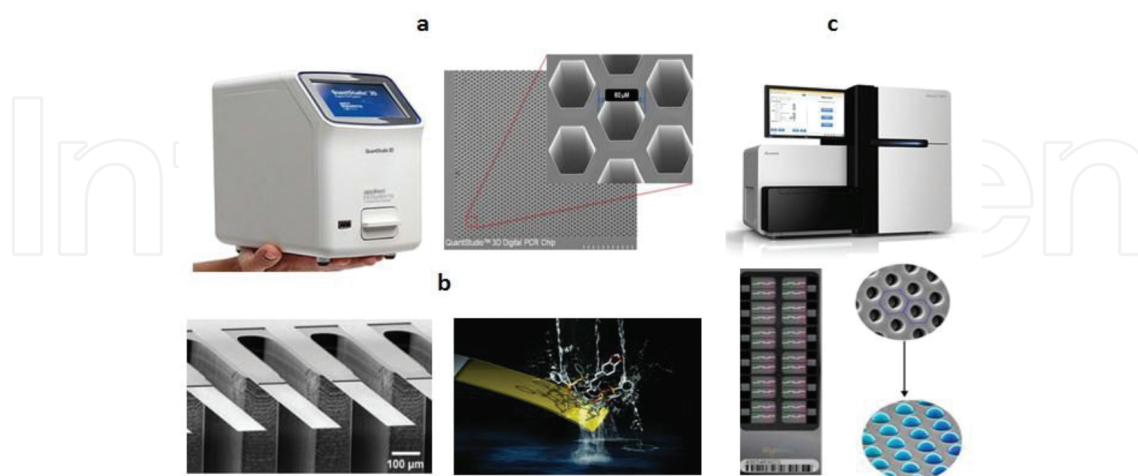
From research development to microfluidic platform applications and product transfer, a holistic and seamless strategy has to consider from the start point to the end. The right selection of the material interface, which might be suited for certain targeted applications, can be detrimental for another purpose. Therefore, navigating material sciences for microfluidic technology is somehow a nebulous nightmare. These difficulties are also enhanced according to the fact that these microfluidic techniques were developed by the physics and engineering landscapes involved in information technology (IT) research and development (R&D), and therefore they exploited silicon-based clean room technologies. The lack of an adequate material culture related to biomaterials and polymer-based microstructure induced obvious limitations, which is a significant inhibiting factor for further industrial transfers. Besides the complexity and the interdisciplines involved in microfluidic applications, where bioengineering, microbiology, microfluidics, optics, materials science, and electrochemistry are concerned,

proper and deep understanding and paradigms of each community are a must for any achievement of a significant system. Still at its early age, microfluidic science and technology have already made successful demonstrations addressing the issues; however, this knowledge is still mostly limited to chemistry, biology, and physics researchers; and unfortunately, it has not sufficiently penetrated yet the biomedical research and clinical environments. The goal of this chapter is thus to fill the gap and promote pertinent highlights on materials performance for microfluidic applications.

Legacies from microelectronics industry and the glassware history in biomedical and chemistry areas, both silicon and glass materials, constitute the initial materials for microfluidic device fabrication. Currently, materials dedicated to microfluidics can be categorized into three broad groups: inorganic, polymers, and paper. Beyond silicon and glass, inorganic materials extend over co-fired ceramics and vitroceraamics. The second polymer-based category can be divided into two subcategories (i) thermoset materials, which are thermal or UV curable materials from a low viscosity precompound dispensed over a mold and (ii) thermoplastic materials, which are thermoformable materials amendable for rapid prototyping and manufacturing. Both polymer subcategories display rigid to elastomer mechanical properties, and through adaptable formulation and enriched chemical modification, offer a broad range of physicochemical surface properties. Finally, paper microfluidics is an emerging technology based on a patterning approach, where devices drive liquid through capillary actions via wicking in a cellulose matrix.

## 2.1. Inorganic materials: silicon, glass and ceramics

Silicon was the first material used for microfluidics [1]. Indeed, in the mid-80s, the microelectromechanical systems (MEMS), from which microfluidic technology is one of the branches that handle fluid, were developed by microelectronic technology. In MEMS, silicon material



**Figure 1.** (a) QuantStudio 3D Digital PCR system from Life Sciences and its silicon chip, 60  $\mu\text{m}$  hexagonal wells organized in a honeycomb structure. (b) Array of Si cantilevers for label-free biodetection of illicit drugs in water. (c) Next generation sequencing HiSeq 2000v3 system developed by Illumina and the silicon chip for microbeads immobilization.

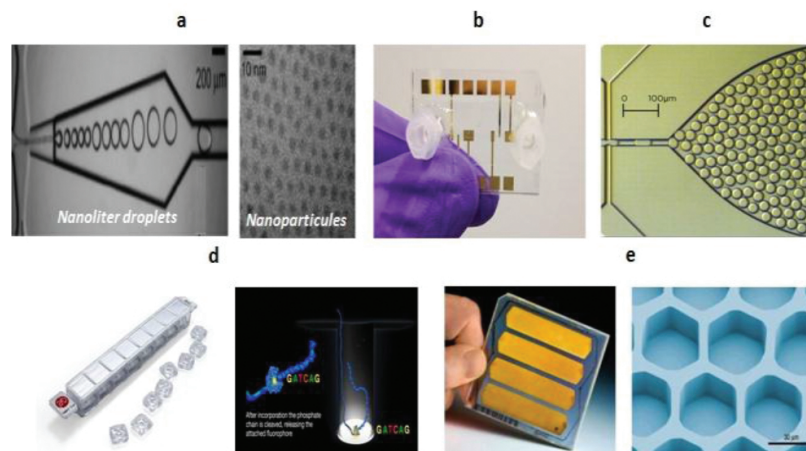
was the standard material interface. Fabrication of silicon and glass devices involves either subtractive methods (e.g., wet and dry etching) or additive methods (such as metal/dielectric/insulate deposition). Silicon surface chemistry based on the silanol group (-Si-OH) is also well developed and large panels of surface biochemical modification accomplished via silanes chemistry are accessible. Silicon displays a high elastic modulus (~150 GPa) and so, in such a way, active pumping and valving integration, as well as Si brittle characteristics induced overall fragility. Therefore the narrow windows of mechanical properties are limiting factors. Transparent to IR light, but not in visible range, can cause serious issues and limitations that are obvious for biological fluorescence-based optical detection methods and for direct fluid imaging. Those issues can be partially solved via several hybrid system approaches, where Si channels can be sealed with transparent materials, such as glass or polymers, leading to a renaissance for Si-based detectors for microfluidic systems. However, Si microfluidic systems, where reagent storage and other embedded biochemical surface functionalization (e.g., DNA, proteins and cells patternings) are required, feature limitations when considering final assembly and package steps. Indeed, high pressure, temperature, and voltage constraints induced complex strategies for overall device integration concerns. Current approaches such as reactive ion etching (RIE) for plasma exposure in order to activate surface for sealing purposes or high temperature, high pressure parameters for anodic bonding methods are definitively not suitable when considering reagent integration, such as proteins, cells, and nucleic acids species. Even recent efforts developed by Ruchi et al. [2], who reported a low-temperature bonding strategy and Si-Si interface bonding at low-voltage direct current of about 80 V, the procedure was still performed at a processing temperature of 365°C. For the aforementioned strategy, where a hybrid system is implemented, the definite air-tight and water-tight sealing achievements, which are also of priority for biomedical applications considering contamination issues, suffer from the rather similar limitations. Indeed, hybrid approaches in most cases currently consist of realizing a pressure-free soft contact with the rigid silicon part that needs either oxygen plasma exposure or thermal treatment for sealing and device completion. However, at the research level, due to the high resolution of Si nanofabrication capabilities realized by either electronic beam or nanoimprint lithography among others, and its enriched surface chemistry means for biomolecular grafting, the following highly representative examples and significant achievements for the microfluidic community are highlighted. Applications related to the high-resolution capabilities of silicon extend over plasmonic, resonators, and microcantilevers systems. Indeed, high-quality nano-optomechanical resonators exhibiting mass sensitivity at the attogram level in the flow through operating environment have already been reported [3]. Si plasmonic microarrays have been interfaced for real-time and label-free monitoring of biomolecule interactions of A/G with immunoglobulin G (IgG) antibody [4]. Finally, as a tremendous achievement for the Si-based microfluidic approach, beyond the aforementioned limitations, we wish to underline the obvious advantages of the stationary Si-based system for complex digital qPCR platforms for genomic applications. Quantitative determination of pathogenic loads with such Si platforms definitely opens an area for medical research that benefits patients. In comparison to low-cost and single-use POC (Point-of-care) devices for decentralized purposes, where challenges involved with silicon materials imposed challenging technical needs, Si interface and glass are

strategic materials of interests for stationary and highly complex systems. **Figure 1(a)** presents the QuantStudio® 3D Digital PCR system and the related silicon chip developed by Life Sciences Technologies Inc. (St. Petersburg, FL, US). We also refer the readers to the silicon EWOD qPCR platform developed by Gidrol et al. [5] and for further interests to a recent review by V. Marx [6]. Finally, the silicon interface is the material of reference for the vast majority of nanomechanical biosensor [7] systems based on the cantilever approach as illustrated in **Figure 1(b)**. Recently, an array of Si cantilevers for label-free biodetection of illicit drugs in water has been reported [8]. For next generation sequencing (NGS) purposes, **Figure 1(c)** displays the HiSeq 2000v3 system developed by Illumina Inc. (San Diego, CA, US) and the silicon chip realized for microbeads immobilization.

Besides Si, glass, due to its wide applications in chemistry has been adopted as a key material for lab-on-a-chip fabrication. Optically transparent with excellent and low-fluorescence background, glass also displays highly suitable chemical resistance. Thus it has emerged as a material of choice. Its transfer to microfluidics has been facilitated due to the traditional “off-chip” chemistry developed over several decades. Glass microfabrication involves well-established processes such as UV photolithography and chemical etching; however, such technologies rank relatively low when considering further manufacturing perspectives, compared to rapid thermal molding technology for polymer-based microfluidic system. It is for this reason the glass is generally viewed as an application material. Conversely, it may be easier and potentially less cost effective to fabricate small number of microfluidic devices in glass than making molds for replication purposes using polymer-based systems. The chemical and thermal properties of glass enable a wide range of functions to be undertaken on the device, including the requiring aggressive and corrosive solvents, chemical agents, and others extreme temperature applications. Finally, assembly, conditioning, and on-chip reagent storage steps suffer similar limitations to the Si material. In particular, the glass fusion bonding is extremely slow and requires very high temperature. However, for high-pressure demanding applications associated with its strength, maintaining high level of channel integrity over operation, glass is definitively positioned at the preferred place. Compatible with electrophoretic-based separation techniques, microfluidic glass chips have been used for numerous demonstrators and coupled to either mass spectroscopy, electrochemical, or chemiluminescence detection means among others. From peptides to vascular biomarkers and DNA identification, we refer the reader to recent comprehensive reviews on advances for glass  $\mu$ CE chips [9, 10]. Glass mostly used the microfabrication approach that involves standard UV photolithography in combination with either dried or wet etching protocols. Frequently used wet etching chemical solutions feature a significant isotropic etchant property, therefore, the achievement of microchannels with straight and high aspect ratio structures are challenging. Alternative etching profiles such as anisotropic or straight-walled patterns can be done with dried RIE processes. Micromilling of glass is the second-most used approach. It is a subtractive process, where a rotating cutting tool removes material from a workpiece. Compared to micromilling of polymers, more attention for glass is required. This is primarily due to its high hardness and low tensile strength. Most milling is done using computer numerical control system (CNC micromachining), which represents a great deal of opportunity and flexibility in terms of pattern generation. However during processing, overheating of the diamond-

coated drilling tool has to be considered, and cooling strategies therefore are implemented. Definitely, CNC micromachining offers a high level of interest for rapid prototyping of glass microchip, we refer the readers to the recently published micromilling tutorial review [11, 12].

Illustrating the high-performance capabilities of the glass interface for highly demanding applications, **Figure 2(a)** presents the microchip developed by Chan et al. [13] for the high-temperature synthesis of CdSe nanoparticles in nanoliter-volume droplets in a perfluorinated fluid carrier. **Figures 2(b)** and **(c)** highlight the recent efforts by Klearia (Marcoussis, France) and Dolomite (Royston, UK) companies for the development of low-temperature bonding protocols for embedded technologies. Finally, related to the development of NGS technologies, **Figures 2(d)** and **(e)** depict the glass chips made by Pacific Biosciences (Palo Alto, CA, USA) and Roche Diagnostics (Indianapolis, IN, USA) for their single molecule real-time sequencing technology (SMRT) and their 454 sequencing systems, respectively. Distributed by Weill Cornell Medical Researchers (Ithaca, NY, USA), each SMRT cell is provided at a cost of \$ 400.



**Figure 2.** (a) Glass chip for high-temperature (300°C) synthesis of CdSe nanoparticles from nanoliter-volume droplets. (b) Array of Si cantilevers for label-free biodetection of illicit drugs in water. (c) High demanding (500°C and 300 bar) glass chip for droplet generation form dolomite. (d) Pacific Biosciences single molecule Real-Time Sequencing glass chip. (e) Glass PicoTiter plate for DNA sequencing systems from 454 DNA sequencing system.

Ceramic microfluidic platforms can be fabricated using low temperature co-fired ceramic (LTCC) technology for the achievement of hermetically sealed monolithic microfluidic platforms with homogeneous surface chemistry and physical properties through a pertinent cost-effective manner compared to Si and glass platforms. This is a well-established technology for low-cost and high-volume production of portable wireless electronic applications, but yet with limited involvement into the microfluidic landscape. However, its multilayer fabrication approach allows monolithic integration of complex structures. As a result, three-dimensional microfluidic channels and cavities have been already reported [14]. The compatibility with ink printing techniques has enabled the development of highly integrated devices that incorporate electrochemical detection as well as all the electronic components for signal and data processing [15]. However, the integration of optical detection means in such platforms still constitutes a serious issue due to the overall opacity of ceramic material. To mitigate this issue, two

strategies have been implemented: (1) the integration of optical fiber and (2) the implementation of transparent windows for localized optical analysis [16]. Recently, Microresist Technology Inc. (Berlin, Germany) developed a promising and organically modified ceramic Ormocer as an optically transparent and UV curable ceramic material to fix this issue.

## 2.2. Polymers: thermoset and thermoplastic materials

In the last 15 years, polymers have played the leading role from prototyping and manufacturing perspectives. This is because they offer a broad range of physical and surface chemical properties through adaptable formulation and enriched chemical modification. Based on their adhesiveness intrinsic properties, or activated bonding strategy, complex and 3D multilayered systems have been implemented. Considering both the cost of raw materials and manufacturing perspectives, several polymer interfaces, but none of all, are amendable to mass production processes (e.g., hot-embossing, injection-molding, and roll-to-roll). For the aforementioned thermoset subcategory, the most common materials are thermal and UV curable materials, Respectively, polydimethylsiloxane (PDMS) and the so-called SU-8 photoresist [17, 18]. On the thermoplastic side, the most popular materials are polycycloolefin (PCO), polycarbonate (PC), polytetrafluoroethylene (PTFE) and polystyrene (PS). Polycyclo-olefin offers high moldability and low water uptake [19, 20]. Polycarbonate [21] has excellent material toughness properties while polytetrafluoroethylene [22] and polyimide [23, 24] feature excellent chemical resistance, electrical, and thermal properties, respectively. Polystyrene has become more and more involved for cellular-based microfluidic systems, due to its wide applications in cell biology. Indeed, PS has provided decades of conclusions and sensitive protocol establishment, and numerous cell behaviors and functions have been determined [25]. Currently, PDMS and a dozen thermoplastic materials cover the vast majority of microfluidic research activities. The intensive use of PDMS is devoted to rapid prototyping and proof-of-concept demonstrations. However, despite its intrinsic drawbacks, mainly related to its cellular toxicity, molecular adsorption and absorption, gas permeability, and bonding issues, PDMS still appears as the preferred material in laboratories. Its industrial transfer is generally not overly recommended due to the cost concern. On the other hand, although thermoplastic interfaces offer the solution for product development, the entry cost in terms of required mold making as well as equipment setting limits its development. In addition, only well-established groups have significant infrastructures and facilities to afford it. To end this section, recently introduced soft thermoplastic elastomers (sTPE) are discussed. These materials bridge the gap between PDMS and classical rigid thermoplastic materials such as PC, PCO, and PS [48–52]. The sTPE materials are low-cost and commercially available polymers, offering transparency, biocompatibility, and flexibility compared to PDMS, and they can be rapidly thermoformed like currently used thermoplastics. Additionally, they display enhanced molding properties; indeed, low-pressure molding can be performed (e.g., <1–2 bar), lowering down the thermomechanical properties of the required molds. Due to their elastomeric properties, they can easily be peeled off from the mold. Assembling and bonding procedures are more convenient, and cohesive sealing can be done without thermal and/or plasma treatment. This material promotes a seamless integration, promoting therefore a realistic transfer path from prototyping to feasible and realistic industrialization. The sTPE



material could become a mainstream platform for microfluidic technology and POC applications.

### 2.2.1. Thermoset

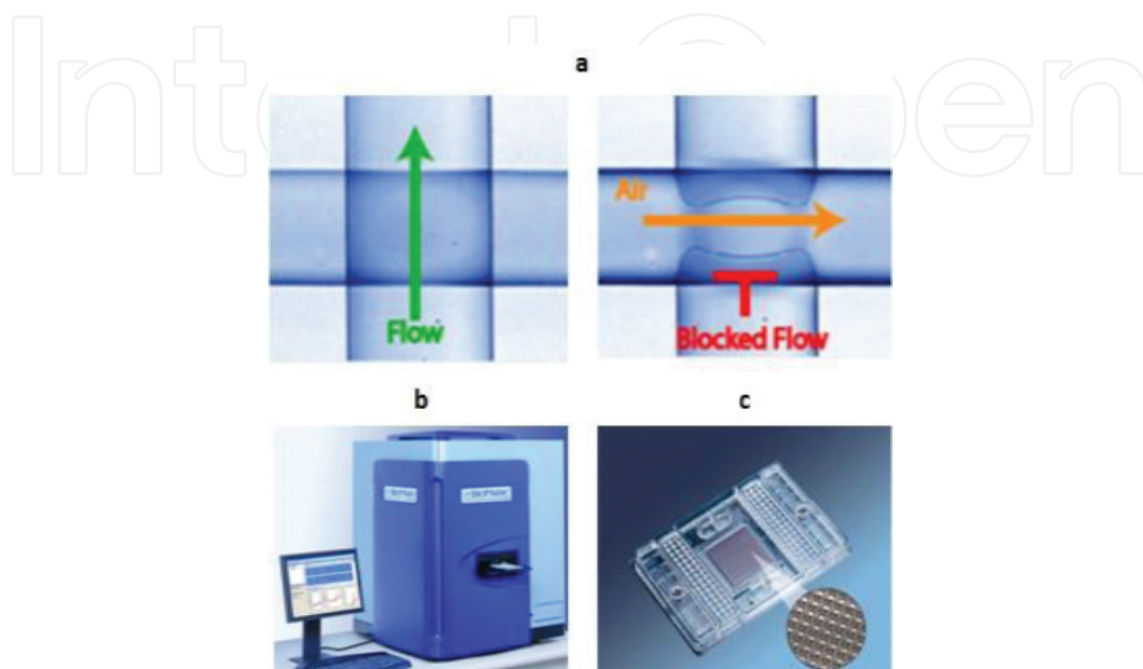
Thermosets are liquid or solid materials at room temperature. Their molecular polymer chains cross-link through a process called curing, when the polymer is heated or exposed to light or to others radiations. The curing step involves an irreversible chemical reaction. Therefore once formed, the thermoset parts cannot be reshaped anymore. Typical examples of thermoset polymers used in microfabrication are PDMS and SU-8 materials.

### 2.2.2. PDMS

First introduced in the late 90s, PDMS [26] is the most common microfluidic substrate, a large portion (40–45%) of research papers published on microfluidic devices utilizes this material [27]. Devices' molds are formed via traditional micromachining and photolithography means and a mixture of two liquid polymer components are mixed together and then casted, cured, and finally peeled off from the master. Due to its elasticity, integration of microvalves or micropumps is possible, and complex 3D system and numerous point-of-care devices have been developed for research applications. PDMS displays excellent optical properties for convenient fluorescence detection and fluid imaging. Due to its gas permeability, PDMS appears as a material of choice for many but not all cellular studies.

On the other hand, four important properties of PDMS have negative impacts: (1) channel deformation due its high mechanical compliance, (2) evaporation and absorption, (3) leaching-out of uncrosslinked oligomers, and (4) hydrophobic recovery [25]. The compliance issue is particularly true considering cell culture experiments that require accurate control over shear force on the endothelial monolayer, the inability to account for mechanical deformation bias in data analysis and subsequent data interpretation [28]. Oxygen permeability in PDMS is three orders of magnitude higher as compared to PS, and may in fact produce a hyperoxic micro-environment leading to cellular stress [29, 30]. Water vapor resulting from the permeable PDMS also leads to problematic shifts on volumes, concentrations, and chemical balances [31]. PDMS is also largely prone to bulk absorption of hydrophobic compounds. Regehr et al. [32] have shown significant depleted estrogen levels in culture media, leading to inhibition of protein-1 activator. Similarly, important shifts were identified in response to fluoxetine over transfected human embryonic kidney (HEK) in between PDMS and polystyrene interfaces [33]. Finally, absorption not only affects fundamental cellular biology on chip, but also drug discovery and high-throughput screening applications. However, the PDMS abilities to provide rapid (1–4 h), easy, low-cost (50–200 \$/kg) and straightforward accessibility make it a major leading player for prototyping uses at academic level. However, its commercial applications are generally avoided. A noticeable exception emerges from this mainstream Eration, indeed around the multilayered PDMS pressure-actuated crossed-channel valve architecture initially developed by Quake et al. [34]; the Fluidigm company (San Francisco, CA, USA) has developed several impressive applications ranging from qPCR platforms to mass cytometer as depicted in **Figure 3(a)** and **(b)**. Such system can run 48 samples in 770 reaction chambers.

Each chip shown in **Figure 3(c)** ranges at a cost from \$ 400 to 800. This price highlights the intrinsic and overall PDMS difficulties and its lengthy processing steps to tackle for low-costs microfluidic system for single use perspective. We refer the readers to the following reviews for extended discussion related to microfluidic products development and the ambiguous positioning of PDMS material in the community for applications development [25, 35, 36].



**Figure 3.** (a) Bilayer PDMS pneumatic valving microfluidic system, liquid flow inside the vertically oriented top channel and the bottom channel (air flow) is pressure-actuated for clogging/or liquid motion of the fluidic layer. (b) and (c) Biomark HD system for digital qPCR from Fluidigm, which run 48 samples in 770 reactions/sample chip.

### 2.2.3. SU-8: an epoxy-based material

Using classical means of photolithography or stereolithography, SU-8 microfluidic devices can be built in a complex 3D structure out of an initial liquid resist. SU-8 contains eight epoxy groups which undergo a very strong crosslinking upon exposure to UV light. Such composition and process lead to highly mechanically, thermally, and chemically stable materials. However, large internal stress exists due to the process, providing thus an overall brittle characteristic, and therefore making it difficult in handling and transferring part. SU-8 can be deposited and patterned in a range of thicknesses from nanometer to millimeter films, using lithography (either UV and e-beam), the lateral feature resolution extends from the macroscopic surface down to submicrometer. SU-8 can be structured also from the laser ablation approach. However, as for photolithography means, it appears that both methods have limited throughput [37]. Indeed, the cycle for resin preparation and others processes are lengthy. It seems that SU-8 is limited mainly to academic uses. For in-depth descriptions of the SU-8 interface for microfluidic applications, we refer the reader to a couple of comprehensive and exhaustive reviews [18, 38]. Beyond its use for direct microfluidic device fabrication, SU-8, due to its high mechanical strength and its capabilities to create high aspect ratio structures [39]

and complex 3D networks [40], is definitely a material of choice for mold master making. The SU-8 mold has been intensively used for hot-embossing of thermoplastic devices, or as an intermediate system for injection-molding [41].

#### 2.2.4. *Alternative thermoset material*

Besides PDMS soft thermoset material, several attempts have been introduced in order to provide alternatives for soft thermoset materials and mainly the use of fluorinated-based polymers has been reported. The attractiveness of those solutions arises from the inertness of the perfluorinated compounds. De Simone et al. [42] have developed a photocurable soft perfluoropolyethers (PFPE). It exhibits low toxicity and low surface energy and displays enlarged chemical resistance. For multiphasic microfluidic environment, it might be a material of choice due to the fact that such Teflon-like structure is both oleophobic and hydrophobic. More recently, high aspect ratio (up to 6.5) PFPE microfluidic devices have been fabricated by a direct photolithographic process. Through a mask-assisted photopolymerization approach, the authors have successfully developed a rapid overall process of around 5 min and demonstrated important sealing capabilities, indeed the device can withstand a pressure up to 3.8 bar [43]. Finally, the devices have been tested with some model reactions employing organic solvents.

#### 2.2.5. *Thermoplastic polymers*

##### 2.2.5.1. *Rigid thermoplastics*

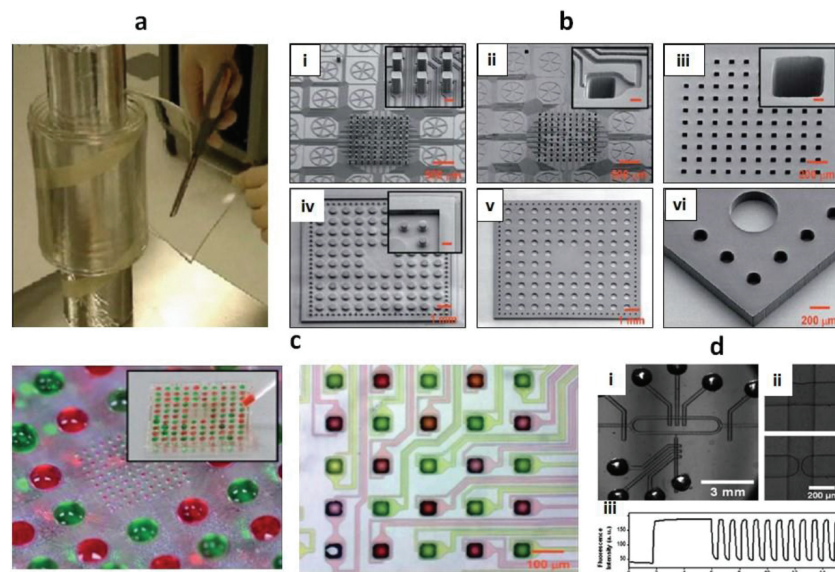
According to the aforementioned drawbacks of PDMS, intensive use of thermoplastic materials, such as polycarbonate and polystyrene, is increasing. These materials are amendable for rapid thermoforming manufacturing technology in the CD and biology industries. Those platforms have been clearly identified as materials of choice for microchip research and subsequent technology transfer. Complementary polymethylmethacrylate (PMMA) and polyimide, due their favorable position in the semiconductor industry, complete the set of foreseen thermoplastic candidate. More recently, polycyclo-olefin polymer has become another popular substrate for microfluidics. It displays high chemical resistance, low water absorption, and excellent optical transparency in the near UV range. The materials are moldable polymers when heated above their glass temperature, offering thus recyclable and reshaping perspectives. They also provide a subsequent bonding pathway. They are optically clear and commercially available, and they display slightly better solvent compatibility than PDMS. However, they are incompatible with most organic solvents, such as ketones and hydrocarbons. Currently used thermoplastic interfaces are rigid and stiff materials with Young modulus in the range of Giga Pascal. Consequently, they are not as convenient as PDMS to achieve conformal contact. Therefore, sealing strategies involve pressurized solvent-assisted and thermal approaches to melt surfaces. In addition, the following thermoplastics: perfluoroalkoxy (Teflon PFA) and fluorinated ethylenepropylene (Teflon FEP) can be used for extremely inert microfluidic devices. Ultimately, they feature nonstick and antifouling properties. PFA has been used for high-quality immobilization of *Escherichia coli*, *Pseudomonas*

*putida*, and *Bacillus subtilis* cells in highly dense microarray patterns [44, 45]. For more classically used interfaces, Zhang et al. [46] reported sealing and chemical surface modification of an integrated monolithic PMMA microdevice for DNA purification and amplification of *E. coli*. Also, a highly integrated polystyrene microfluidic chip coupled to electrospray ionization mass spectrometry for on-chip protein digestion and online analysis was developed [47]. One of the most important challenges faced when targeting for molding of thermoplastic parts is the realization of the master cavity featuring submicron resolution, high aspect ratio, and densely packed structure areas. Most of the materials are crystalline and/or semi-crystalline, and they display high coefficient of thermal expansion (CTE) and high shrinkage parameters compared to amorphous ones. Additionally, due to the fact that they are rigid and often brittle, they represent sensitive challenges from the manufacturing perspectives. The high shear force resulting from the pressurized environment generates asymmetric and/or random pull-off of plastic edges due to friction in demolding, which is downstream detrimental for sealing and bonding. The characteristics of the thermoplastic materials induce high specifications on the thermo-mechanical properties of the master molds. Currently, the impacts on the master mold making related to the realization of such thermoplastic parts are only metallic (stainless, nickel-cobalt alloy, and aluminum), and from prototyping perspectives, only few epoxy molds can be employed. Even if elegant CNC laser machining and electroplating processes are available for mold making, the implementation of such master are expensive and are limited in terms of resolution, pattern density, and aspect ratio. The work suggest an overall in-depth consideration when starting to envisage a microfluidic system development, undoubtedly a holistic approach should be taken. The overall chip constraints in terms of fabrication, sealing, packaging, thermomechanical loads, biological compatibility (both in terms of physicochemical surface properties and reagent integration), biomicrofluidic functions, microfluidic statistical, and robust properties have to be considered.

#### 2.2.5.2. Soft thermoplastic elastomers: sTPE

The sTPE is a class of material in which elastomeric properties of elastomer rubber (e.g., PDMS) are embodied with the ease of processing of thermoplastic materials such as PMMA, PCO, and PC. The sTPE thus bridges the gap in between thermoplastics and elastomers, enhancing the advantages of each material. Moreover, the range of sTPE Young modulus extends continuously from 0.1 MPa to 1–5 GPa. The combination of elastomeric and thermoplastic properties makes these materials potential substitutes to PDMS and/or hard TP polymers that are commonly employed in microfluidics [48]. Unlike PDMS, sTPE can be used in the form of extruded sheets that provide off-the-shelf availability without the need of performing any precompounding step. Extruded films can be stored over a long period of time (e.g., several years) without any notable degradation, making it possible to use the material on demand at any time (**Figure 4(a)**) [49, 50]. The sTPE materials are available at low cost, and they display optical transparency and biocompatibility for proteins, nucleic acids, and cell and tissue engineering and diagnostics [49–53]. sTPEs are block copolymers comprising different monomer sequences that are distributed randomly or statistically in domains through diblock or triblock architectures [51]. For styrenics-based sTPE materials with low PS content (10–12%), thermodynamic incompatibility between blocks induces

nanophase separation and self-assembly of PS domains into nanometric clusters (typically 10–30 nm in diameter) that are distributed in a three-dimensional fashion within a hexagonal symmetry in the rubber matrix of ethylene-butylene (EB). This morphology provides the basis of the material performance: rigid PS domains act as junction points that stabilize the polymer matrix while the EB-dominant phase offers elastomeric properties. Moreover, size and cluster distributions promote the sTPE surface to be uniform and homogenous at the microfluidic device level [49–53]. As block copolymer materials, sTPE exhibits two glass transition temperatures corresponding to the EB soft block ( $T_{g,EB} \sim -60$  to  $-75^\circ\text{C}$ ) and to the styrene rigid block ( $T_{g,EB} \sim -90$  to  $105^\circ\text{C}$ ), respectively. The negative value of  $T_{g,EB}$  predicts liquid-like behavior of the materials.



**Figure 4.** (a) Photograph of an extruded flexestene foil on a roll from which pieces can be cut conveniently before use. (b) Series of SEM images illustrating the fabrication of the microfluidic flexestene device. (i) SU-8 embossing mold used for the fabrication of the bottom flexestene membrane, (ii) Upper and (iii) lower side of the bottom sTPE membrane, (iv) SU-8 mold used for the fabrication of the top sTPE membrane, (v) overview, and (vi) close-up view of the top flexestene membrane. Scale bars in the insets of (i), (ii), (iii), and (iv) correspond to 50, 20, 10, and 200  $\mu\text{m}$ , respectively. The images shown in (iv) and (v) were assembled from several SEM micrographs to achieve the desired field of view. (c) Photographs of an assembled 3D microfluidic immobilization after filling with solutions of a red and green dye (left), optical microscope image of the resulting red-green pattern obtained on the central region of the microfluidic device (right). (d) high-throughput fabrication method of sTPE multilayered microfluidic devices, (i) Optical micrograph of the whole micromixer made of two layers of sTPE material bonded on a poly(cyclo)olefin polymer substrate. The device size is smaller than a centimeter square, and each valve measures  $200 \mu\text{m} \times 200 \mu\text{m}$ , (ii) detailed view of a valve at both open and closed positions; and (iii) curve representing the valving cycle at 1.2 Hz, fluorescence intensity under the deflected membrane is registered, it is maximal when the valve is open and minimal when closed.

Indeed, like PDMS, which similarly displays a negative glass transition temperature, the selected sTPE forms a spontaneous and conformable close contact with flat substrates, generating tight air and water sealing [49–53]. Additionally, the soft blocks provide bonding capabilities above their glass transition, which implies that even at room temperature, the polymer chains can be reorganized according to the contact surface. The bonding strength is variable and dependent on time and temperature; and irreversible bonding was obtained at

room temperature [50, 52]. Depicting the enhanced molding capabilities of sTPE interface, Brassard et al. [51] have demonstrated the rapid and reliable patterning of open through-hole microstructures in sTPE material using a method based on hot-embossing (**Figure 4(b)**). The sTPE-based 3D microfluidic patterning device was then used for the immobilization of up to 96 different biological probes in a 10×10 array format of 50 μm×50 μm spots (**Figure 4(c)**).

Additionally, for novel tissue engineering biomaterial platform, high molding performances have been confirmed in a newly reported process. We reported a rapid microfabrication of a biocompatible sTPE sheet in an overall 3 min process operating within an ultralow applied pressure (1.6 bar) [52]. Smooth muscle cells contact guidance studies have been conducted over an array of 4-μm-patterned grooves [52]. For reader's information, contributing to the establishment of the biocompatibility, the bonding and the microfabrication performance of sTPE, which are highly dependent on block copolymers formulation (molecular weight of each block of each diblock (DB) and triblock (TB) and the DB/TB ratio) and also to the additives composition (tackifiers and processing agents); we underline the Flexstene sTPE materials performance (InfineFlex Inc., San Diego, US and Blackholelab Inc., Paris) for the fabrication of adjacent micropillar arrays with different heights for cellular studies [53]. We also demonstrated that sTPE can be used as a rapid technique for the fabrication and assembly of pneumatically driven valves in a multilayer microfluidic device using a simple SU-8 mold material for embossing purposes (**Figure 4(d)**) [54]. The quality of the obtained soft thermoplastic valve shows a robust behavior with an opening–closing frequency of 5 Hz. Finally, more recently [49], we demonstrated the implementation of a sTPE CD-like microfluidic system for genomic assay. This device integrates all required molecular assay steps, from cellular lysis to gDNA polymerase chain reaction amplification, amplicons digestion, and microarray hybridization on a plastic support. The low-temperature, pressure-free assembly and bonding of sTPE material on the flat polyolefin thin substrate offer a pertinent solution for simple and efficient loading and storage of the required on-CD board elements. This was demonstrated through the integration and the conditioning of microbeads, magnetic discs, and dried enzyme species. This work highlights a seamless strategy that promotes a feasible path to transfer from prototyping toward realistic industrialization. This work aims to establish the full and pertinent potential for sTPE centrifugal system as a mainstream microfluidic diagnostic platform for clinical molecular diagnostics, water and food safety, besides other applications.

## 2.3. Paper, biodegradable and hydrogel materials

### 2.3.1. Hydrogels

Hydrogels display a molecular architecture analog to extracellular matrix, with water uptake properties up to 80% of its total mass. Hydrogels are highly porous and thus an excellent matrix for cellular biology studies. However, direct tissue engineering from bulky hydrogels are challenging due to the restricted depth for nutrients diffusion of around hundreds micrometers [55]. Microfluidic technology, through both top-down and bottom-up approaches, has demonstrated its abilities to tackle this fundamental issue. From a top-down approach, microchannels are fabricated inside the hydrogel while for the bottom-up, hydrogels filled

microchannels cavities. Matrigel™ and collagen are the mostly used animal-derived hydrogels. They promote excellent cellular adhesion and proliferation [55]. Recently, Bang et al. [57] engineered a 3D neural circuit in a microfluidic Matrigel hydrogel system. They had grown, aligned, and organized 3D networks of axon bundles at an average speed of  $250 \mu\text{m} \cdot \text{d}^{-1}$  for a period of 6 *in vitro* days. Alternatively, alginate and agarose plant-derived hydrogels and synthetic ones, such as polyacrylamide or polyethylene glycol (PEG), can be used [58]. Even though synthetic hydrogels slightly lack cellular adhesion compared to animal-derived ones, they nevertheless promote higher flexibility and enriched formulation adaptability for fine tuning objectives. Hydrogel composition, structure, morphology, and rigidity have been used in a high-throughput manner in droplet-based microfluidics [59]. Recently, agarose hydrogels have been integrated in a microfluidic system for *E. coli* purification and concentration, and finally for fluorescence immune detection. Authors reported that 90% recovery efficiency could be achieved with a million-fold volume reduction from  $400 \mu\text{L}$  to  $400 \text{pL}$ . For concentration of  $1 \times 10^3 \text{ cells mL}^{-1}$  bacteria, approximately ten million-fold enrichment in cell density was realized. Urine and blood clinical isolates were further tested and validated [60]. We refer the readers to follow the review for further reading [61].

### 2.3.2. Biodegradable materials

Biodegradable polymers for tissue engineering and drug delivery purposes display degradation time ranging from 24 h to several months. They offer, in a microfluidic format, a promising opportunity for microstructured tissue scaffolds. Commonly used biodegradable matrices are polycaprolactone, poly(lactide-co-glycolide), and polyglycolic acid (PGA). Their degradation and mechanical properties are tunable, and they display minimal changes in the systemic immune responses. Their degradation products such as glycolic acid for PGA are through metabolite response absorbed by the hosted living body. Curing of these materials takes place as their dimer version polymerizes via a ring-opening reaction under appropriated heating and catalytic steps. An excellent review related to biodegradable material properties and their microenvironment integration has been recently published [62]. Various technologies, such as printing, soft-lithography, stereolithography, hot-embossing, and injection-molding methods, have been used toward integration [63, 64].

### 2.3.3. Paper

Paper is the most recently introduced microfluidic material. Its cellulose matrix acts to wick liquids while specifically, hydrophobically, patterning areas to avoid liquid motion. The patterned barriers define the shape (i.e., width and length) while the thickness of the paper accounts for the height. Hydrophilic wicking regions thus serve as channel networks opened to air. Paper as chip material is one of the cheapest materials, and it can be easily stacked in 3D devices [65]. The fabrication approaches can be divided into two groups. Lithographic-based methods, where particular coated polymer areas are removed, thus are forming the channels. Second, the printing and the cutting approaches allow direct hydrophobic barrier definition without exposure of the effective channels to any reagents. Fundamentally, paper-based microfluidic systems are not suitable for large-volume samples and their applicable

detection perspectives are limited owing to the intrinsic cellulose matrix properties. Recently published by Mace et al. [66], paper-based diagnostic devices and their manufacturing perspectives are commented in detail. Wax printing approaches and assembly of 3D vertical flow assays are further discussed therein. Concerning printing and cutting approaches, the reported channel resolution is quite low and limited to 200  $\mu\text{m}$ . Paper-based technology, displays undoubtedly tremendous limitations considering heterogenous component integration such as valves and other reagent storage issues. Recently, Thom et al. [67] have performed the integration of light-emitting diodes (LEDs) onto paper microfluidic device for the fluorescence detection of  $\beta$ -D-galactosidase. From medium to low complexity bioassay integrations, paper-based technology appears to be a promising pathway for portable and low-cost platform in the future, and thus a material of choice for optimized and multiplexed lateral flow assays in the health care segment. We refer the readers to follow recently published review for further reading on paper-based microfluidic system for bioanalytical applications [68, 69].

### 3. Conclusion

This chapter presents an overview of materials for microfluidic applications and their applications in recent research. The large range of materials dedicated to microfluidics is a key component for successful microfluidic applications. The optimal selection of an adequate material platform for a targeted application is of tremendous importance and represents significant technical challenges. In a concomitant manner, this decision has to be taken accordingly an exhaustive list of requirements essentially related to the biocompatibility, the overall thermomechanical properties, the latter inherent to bonding and reagent integration. Beyond the traditional proof-of-concept works developed at the academic research level, another higher level of concern exists when real applications and medical research are envisioned. Two important issues therefore need to be addressed. First, a reevaluation of the biocompatibility and the overall stability of the intrinsic microfluidic performance when handling real samples. The second aspect involves the scaling-up of each microfabrication, bonding, conditioning, and other packaging needs, and their interdependences and costs. The gap currently is wide in these aspects, and it is one of the most severe limitations for microfluidic applications. Therefore dedicated efforts are needed to tackle this issue. The introduction of sTPE highlights a seamless strategy that promotes a feasible path transfer from prototyping toward realistic industrialization, working from the earliest research steps to the end with a unique polymer interface. Beyond, the polymer materials presented in this chapter, there is tremendous space considering the introduction of other functional polymers in the microfluidic applications. We envision that new research activities focused on conductive, piezo, and magnetically doped polymers among other polymers not only provide a fantastic opportunity for further progress and advancement but also for a new field of research and IP development. The considerations extend surely over new blends of material development for specific goals and needs at large. The high level of multidisciplinary skills required in the field is challenging for the academic community; however, such multidisciplinary nature that extends from biology/medicine, microfabrication, microfluidic materials, and electronic and



optical through sensors also provide unique solutions. Definitely, the development of innovative materials will bring innovations, and our community has to act proactively in this direction for the success of microfluidic research and the real benefit for progress in health-related biomicrofluidic applications.

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## References

- [1] S. C Terry, J. H. Jerman and J. B. Angell, A gas chromatographic air analyzer fabricated on a silicon wafer, *IEEE Trans. Electron. Dev.*, 26(12), 1880–1886, 1979.
- [2] R. Tiwari and S. Chandra, Low-temperature silicon-to-silicon anodic bonding using sodium-rich glass for MEMS applications, *J. Electr. Mater.*, 43(2), 555–566, 2014.
- [3] K. Y. Fong, M. Poot and H. X. Tang, Nano-optomechanical resonators in microfluidics, *Nano. Lett.*, 15(9), 6116–6120, 2015.
- [4] A. F. Coskun, A. E. Cetin, B. C. Galaterra, D. A. Alvarez, H. Altung and A. Ozcan, Lens free optofluidic plasmonic sensor for real-time and label-free monitoring of molecular binding events over a wide field-of-view, *Sci. Rep.*, 4(6789), 2014.
- [5] A. Rival, D. Jary, C. Delattre, Y. Fouillet, G. Castellan, A. Bellemin-Comte and X. Gidrol, An EWOD-based microfluidic chip for single-cell isolation, mRNA purification and subsequent multiplex qPCR, *Lab Chip*, 14, 3739–3749, 2014.
- [6] V. Marx, PCR: paths to sensitivity, *Nat. Methods*, 11, 241–245, 2014.
- [7] J. Tamayo, P. M. Kosaka, J. J. Ruz, Á. San Paulo and M. Calleja, Biosensors based on nanomechanical systems, *Chem. Soc. Rev.*, 42, 1287–1311, 2013.
- [8] E. Biavardi, S. Federici, C. Tudisco, D. Menozzi, C. Massera, A. Sottini, G. G. Condorelli, P. Bergese and E. Dalcanale, Cavitand-grafted silicon microcantilevers as a universal probe for illicit and designer drugs in water, *Angew. Chem. Int. Ed. Engl.*, 53(35), 9183–9188, 2014.
- [9] M. C. Breadmore, R. M. Tubaon, A. I. Shallan, S. C. Phung, A. S. Abdul Keyon, D. Gstoettenmayr, P. Prapatpong, A. Alhusban, L. Ranjbar, H. H. See, M. Dawod and J. P.

Quirino, Recent advances in enhancing the sensitivity of electrophoresis and electrochromatography in capillaries and microchips (2012–2014), *Electrophoresis*, 34(1), 29–54, 2013.

- [10] R. A. Saylor and S. M. Lunte, A review of microdialysis coupled to microchip electrophoresis for monitoring biological events, *J. Chromatogr. A.*, 1382, 48–64, 2015.
- [11] D. J. Guckenberger, T. E. de Groot, A. M. D. Wan, D. J. Beebe and E. W. K. Young, Tutorial review micromilling: a method for ultra-rapid prototyping of plastic microfluidic devices, *Lab Chip*, 15, 2364–2378, 2015.
- [12] F. Z. Fang, X. D. Liu and L. C. Lee, Micro-machining of optical glasses—a review of diamond-cutting glasses, *Sadhana Acad. Proc. Eng. Sci.*, 28(5), 945–955, 2003.
- [13] E. M. Chan, A. P. Alivisatos and R. A. Mathies, High-temperature microfluidic synthesis of CdSe nanocrystals in nanoliter droplets, *J. Am. Chem. Soc.*, 127 (40), 13854–13861, 2005.
- [14] G. A. Grob, T. Thelemann, S. Schneider, D. Boskovic and J. M. Kohler, Fabrication and fluidic characterization of static micromixers made of low temperature cofired ceramic (LTCC), *Chem. Eng. Sci.*, 63, 2773–2784, 2008.
- [15] S. Gomez-de Pedro, M. Puyol, D. Izquierdo, I. Salinas, J. M. de la Fuente and J. Alonso-Chamarro, A ceramic microreactor for the synthesis of water soluble CdS and CdS/ZnS nanocrystals with on-line optical characterization, *Nanoscale*, 4(4), 1328–1313, 2012.
- [16] P. Couceiro, S. Gómez-de Pedro and J. Alonso-Chamarro, All-ceramic analytical microsystems with monolithically integrated optical detection cells, *Microfluid. Nanofluid.*, 18(4), 649–656, 2015.
- [17] S. K. Sia and G. M. Whitesides, Microfluidic devices fabricated in poly(dimethylsiloxane) for biological studies, *Electrophoresis*, 24(21), 3563–3576, 2003.
- [18] S. Arscott, SU-8 as a material for lab-on-a-chip-based mass spectrometry, *Lab Chip*, 14, 3668–3689, 2014.
- [19] A. B. Azouz, S. Murphy, S. Karazi, M. Vázquez and D. Brabazon, Fast fabrication process of microfluidic devices based on cyclic olefin copolymer, *Mater. Manuf. Process.*, 29, 93–99, 2014.
- [20] K. Tsougeni, K. Ellinas, H. Archontaki and E. Gogolides, A microfabricated cyclo-olefin polymer microcolumn used for reversed-phase chromatography, *J. Micromech. Microeng.*, 25, 015005, 2015.
- [21] D. Ogonczyk, J. Wegrzyn, P. Jankowski, B. Dabrowski and P. Garstecki, Bonding of microfluidic devices fabricated in polycarbonate, *Lab Chip*, 10, 1324–1327, 2010.
- [22] M. Salim, G. Mishr, G. J. S. Fowler, B. O’Sullivan, P. C. Wright and S. L. McArthur, Non-fouling microfluidic chip produced by radio frequency tetraglyme plasma deposition, *Lab Chip*, 7, 523–525, 2007.

- [23] H. Mogi, Y. Fukushi, S. Koide, R. Sano, T. Sasaki and Y. Nishioka, Ascorbic acid fuel cell with a microchannel fabricated on flexible polyimide substrate, *IEEE Trans. Sens. Micromach.*, 134, 366–371, 2014.
- [24] A. Zulfiqar, A. Pfreundt, W. E. Svendsen and M. Dimak, Fabrication of polyimide based microfluidic channels for biosensor devices, *J. Micromech. Microeng.*, 25, 035022, 2015.
- [25] E. Berthier, E. W. K. Young and D. Beebe, Engineers are from PDMS-lad, biologists are from polystyrenia, *Lab Chip*, 12, 1224–1237, 2012.
- [26] E. Kim, Y. Xia and G. M. Whitesides, Polymer microstructures formed by moulding in capillaries, *Nature*, 376, 581, 1995.
- [27] H. Becker, Famous last words, *Lab Chip*, 11(13), 2133–2134, 2011.
- [28] J. W. Song and L. L. Munn, Fluid forces control endothelial sprouting, *Proc. Natl. Acad. Sci.*, 108, 15342–15347, 2011.
- [29] J. S. Gewandter, R. J. Staversky and M. A. O'Reilly, Hyperoxia augments ER-stress-induced cell death independent of BiP loss, *Free Radic.. Biol. Med.*, 47, 1742–1752, 2009.
- [30] Y. Tang, E. A. Scheef, Z. Gurel, C. M. Sorensen, C. R. Jefcoate and N. Sheibani, CYP1B1 and endothelial nitric oxide synthase combine to sustain proangiogenic functions of endothelial cells under hyperoxic stress, *Am. J. Physiol.: Cell Physiol.*, 298, C665–C678, 2010.
- [31] E. Berthier, J. Warrick, H. Yu and D. Beebe, Managing evaporation for more robust microscale assays, Part 1, Volume loss in high throughput assays, *Lab Chip*, 8, 852–859, 2008.
- [32] K. J. Regehr, M. Domenech, J. T. Koepsel, K. C. Carver, S. J. Ellison-Zelski, W. L. Murphy, L. A. Schuler, E. T. Alarid and D. Beebe, Biological implications of polydimethylsiloxane-based microfluidic cell culture, *Lab Chip*, 9, 2131–2139, 2009.
- [33] X. Su, E. W. K. Young, H. A. S. Underkofler, T. J. Kamp, C. T. January and D. J. Beebe, Microfluidic cell culture and its application in high-throughput drug screening: cardiotoxicity assay for hERG channels, *J. Biomed. Screen.*, 16, 101–111, 2011.
- [34] M. A. Unger, H. P. Chou, T. Thorsen, A. Sherer and S. R. Quake, Monolithic microfabricated valves and pumps by multilayer soft lithography, *Science*, 288, 113–116, 2000.
- [35] M. I. Mohammed, S. Haswell and I. Gibson, Lab-on-a-chip or chip-in-a-lab: challenges of commercialization lost in translation, *Procedia Technol.*, 20, 54, 2015.
- [36] C. D. Chin, V. Linder and K. Sia, Commercialization of microfluidic point-of-care diagnostic devices, *Lab Chip*, 12, 2118–2134, 2012.
- [37] G. Chantal and M. Khan, Laser processing for bio-microfluidics applications (Part II), *Analyt. Bioanalyt. Chem.*, 385(8), 1362–1369, 2006.

- [38] A. Bertsch and P. Renaud, Special issue: 15 years of SU-8 as MEMS material, *Micromachines*, 6(6), 790–792; 2015.
- [39] R. Daunton, A. J. Gallant and D. Wood, Manipulation of exposure dose parameters to improve production of high aspect ratio structures using SU-8, *J. Micromech. Microeng.*, 22(7), 075016, 2012.
- [40] H. O. Moser and C. Rockstuhl, 3D THz metamaterials from micro/nanomanufacturing, *Laser Photon. Rev.*, 6, 219–244, 2012.
- [41] A. Shamsi, A. Amiri, P. Heydari, H. Hajghasem, M. Mohtashamifar and M. Esfandiari, Low cost method for hot embossing of microstructures on PMMA by SU-8 masters, *Microsys. Technol.*, 20(10), 1925–1931, 2014.
- [42] J. P. Rolland, R. M. Van Dam, D. A. Schorzman, S. R. Quake and J. M. DeSimone, Solvent-resistant photocurable liquid fluoropolymers for microfluidic device fabrication, *J. Am. Chem. Soc.*, 126, 2322–2323, 2004.
- [43] A. Vitale, M. Quaglio, S. L. Marasso, A. Chiodoni, M. Cocuzza and R. Bongiovanni, Direct photolithography of perfluoropolyethers for solvent-resistant microfluidics, *Langmuir*, 29(50), 15711–15718, 2013.
- [44] G. Stojkovića, M. Kriveca, A. Veselb, M. Marinšeka and P. Žnidaršič-Plazla, Surface cell immobilization within perfluoroalkoxy microchannels, *Appl. Surf. Sci.*, 320, 810–817, 2014.
- [45] W. H. Grover, M. G. von Muhlen and S. R. Manalis, Teflon films for chemically-inert microfluidic valves and pumps, *Lab Chip*, 8, 913–918, 2008.
- [46] Y. Zhang, K. T. L. Trinh, I. S. Yoo and N. Y. Lee, Integrated monolithic PMMA micro-device, for DNA purification and amplification of *Escherichia coli* pathogen, *Sens. Actu. B. Chem.*, 202, 1281–1289, 2014.
- [47] X. Hu, Y. Dong, Q. He, H. Chen and Z. Zhu, Fabrication of a polystyrene microfluidic chip coupled to electrospray ionization mass spectrometry for protein analysis, *J. Chromatogr. B.*, 990, 96–103, 2015.
- [48] G. Holden, N. R. Legge, R. Quirk and H. E. Schroeder, Thermoplastics elastomers, 2nd ed. Hanser/Gardner, Cincinnati, 1996.
- [49] E. Roy, M. Mounier, G. Steward, L. Malic, C. Liviu, M. Madou, M. Bergeron and T. Veres, From cellular lysis to gDNA micro-array detection, an integrated point of care thermoplastic CDlab, *Lab Chip*, 15, 406–416, 2015.
- [50] E. Roy, M. Geissler, J. C. Galas and T. Veres, Prototyping of microfluidic systems using a commercial thermoplastic elastomer, *Microfluid. Nanofluid.*, 11, 235–244, 2011.
- [51] D. Brassard, K. Li, M. Geissler, C. Miville-Godin, E. Roy and T. Veres, 3D thermoplastic elastomer microfluidic devices for biological probe immobilization, *Lab Chip*, 11, 4099, 2011.

- [52] M. Guillemette, E. Roy, F. Auger and T. Veres, Rapid isothermal substrate microfabrication of a biocompatible thermoplastic elastomer for cellular contact guidance, *Acta. Biomater.*, 7, 2492–2498, 2011.
- [53] J. Wein, S. Jian, B. Wang, Y. Tan, X. Tu, E. Roy, B. Ladoux and Y. Chen, Fabrication of adjacent micropillars arrays with different heights for cell studies, *Microelectr. Eng.*, 158, 22–25, 2016
- [54] E. Roy, J. C. Galas and T. Veres, Thermoplastic elastomers for microfluidics: towards a high-throughput fabrication method of multilayered microfluidic devices, *Lab Chip*, 11, 3193–3196, 2011.
- [55] N. W. Choi, M. Cabodi, B. Held, J. P. Gelghorn, L. J. Bonassar and A. D. Stroock, Microfluidic scaffolds for tissue engineering, *Nat. Mater.*, 6, 908–915, 2007.
- [56] M. W. Tibbitt and K. S. Anseth, Hydrogels as extracellular matrix mimics for 3D cell culture, *Biotechnol. Bioeng.*, 103, 655–663, 2009.
- [57] S. Bang, S. Na, J. Kim and N. L. Jeon, Engineering-aligned 3D neural circuit in microfluidic device, *Adv. Healthc. Mater.*, 5, 159–166, 2016.
- [58] G. Y. Huang, L. H. Zhou, Q. C. Zhang, Y. M. Chen, W. Sun, F. Xu and T. J. Lu, Microfluidic hydrogels for tissue engineering, *Biofabrication*, 3(1), 012001, 2011.
- [59] M. Chau, H. Thérien-Aubin, Y. Li, Y. Wang, D. Velasco, E. Tumarkin, A. Ramachandran and E. Kumacheva, Microfluidic generation of composite biopolymer microgels with tunable compositions and mechanical properties, *Biomacromolecules*, 15, 2419–2425, 2014.
- [60] Y. Li, X. Yan, X. Feng, J. Wang, W. Du, Y. Wang, P. Chen, L. Xiong and B. F. Liu, Agarose-based microfluidic device for point-of-care concentration and detection of pathogen, *Anal. Chem.*, 86(21), 10653–10659, 2014.
- [61] V. van Duinen, S. J. Trietsch, J. Joore, P. Vulto and T. Hankemeier, Microfluidic 3D cell culture: from tools to tissue models, *Curr. Opin. Biotech.*, 35, 118–126, 2015.
- [62] D. I. Dan Cho and H. Jung Yoo, Microfabrication methods for biodegradable polymeric carriers for drug delivery system applications: a review microelectromechanical systems, *J. Microelectromech. Syst.*, 24(1), 10–18, 2015.
- [63] P. A. Gunatillake and R. Adhikari, Biodegradable synthetic polymers for tissue engineering, *Eur. Cell. Mater.*, 5, 1–16, 2003.
- [64] Y. Lu and S. C. Chen, Micro and nano-fabrication of biodegradable polymers for drug delivery, *Adv. Drug Deliv. Rev.* 56, 1621–1633, 2004.
- [65] H. Liu and R. M. Crooks, Three-dimensional paper microfluidic devices assembled using the principles of origami, *J. Am. Chem. Soc.*, 133(44), 17564–17566, 2011.

- [66] C. R. Mace and R. N. Deraney, Manufacturing prototypes for paper-based diagnostics devices, *Microfluid. Nanofluid.*, 16, 801–809, 2014.
- [67] N. K. Thom, K. Yeung, M. B. Pillion and S. T. Phillips, “Fluidic batteries” as low-cost sources of power in paper-based microfluidic devices, *Lab Chip*, 12, 1768–1770, 2012.
- [68] D. M. Cate, J. A. Adkins, J. Mettakoonpitak and C. S. Henry, Review, recent developments in paper-based microfluidic devices, *Anal. Chem.*, 87, 19–41, 2015
- [69] DY. Xia, J. Si and Z. Li, Fabrication techniques for microfluidic paper-based analytical devices and their applications for biological testing: a review, *Biosens. Bioelectron.*, 77, 774–89, 2016.

