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Review

Polymers for Microfluidic Chips

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Abstract: Microfluidic systems have attracted much research attention recently in the areas of genomics, proteomics, pharmaceutics, clinical diagnostics, and analytical biochemistry, as they provide miniaturized platforms for conventional analysis techniques. The microfluidic systems allow faster and cheaper analysis using much smaller amounts of sample and reagent than conventional methods. Polymers have recently found useful applications in microfluidic systems due to the wide range of available polymeric materials and the relative ease of chemical modification. This paper discusses the fundamentals of microfluidic systems and the roles, essential properties and various forms of polymers used as solid supports in microfluidic systems, based on the recent advances in the use of polymers for microfluidic chips.

Keywords: microfluidic chip, polymer, solid support, gel, photopolymerization.

Introduction

Biotechnology and life sciences have encountered revolutionary changes in the last decade, as MEMS (microelectromechanical system) technologies can be extensively adapted to genomics, proteomics, pharmaceutics, clinical diagnostics, analytical biochemistry and so on. As a result, conventional analytical techniques such as sample separation, sample preparation and detection have been miniaturized and can be performed at micro- or nano-scales on so-called biochips. Biochips allow researchers to obtain massive amounts of information at molecular levels by increasing the performance of conventional methods, resulting in a faster and cheaper analysis. For example, a DNA chip can perform massive parallel analyses of DNA/RNA hybridizations for gene expression or sample screening for single nucleotide polymorphisms.[1,2] A microfluidic chip has multiple functionalities such as sampling, sample preparation, separation, and/or detection, and can also perform faster and cheaper analyses consuming much smaller amounts of samples and reagents than conventional methods.[3-8] These features of biochips are possible due to the miniaturization of many conventional analysis techniques.

A microfluidic chip requires various components to perform multiple functions, including simple microstructures (electrodes, posts, and filters), biological components (pro-

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teins and enzymes), sophisticated sensors and actuators (microstirrers, optical lenses, micropumps, and microvalves), and coating layers (hydrophobic or hydrophilic coatings, self-assembled monolayers). Since most microfluidic chips are designed and developed to analyze biological analytes, the components must be biocompatible. The choice of biocompatible materials is very limited, which often leads to complicated fabrication techniques. One method to facilitate the fabrication of microfluidic chips or their components while overcoming the biocompatibility issues is the use of polymers, as various properties of polymers such as mechanical strength, porosity, and hydrophobicity, as well as biocompatibility, have been extensively studied. In addition, the properties of polymers can be easily modified and altered by changing the constituents of monomers or controlling polymerization conditions. Recently, *in situ* polymerization techniques via photopolymerization in a microfluidic chip have significantly facilitated the fabrication of microfluidic components. This review will briefly introduce the general concepts and features of biochips such as microarray and microfluidic chips, focusing a little more attention on the microfluidic chip. Then, the roles and features of polymers for microfluidic chips, including their essential properties and various forms as solid supports, will be discussed based on the current uses of these polymers for microfluidic chips.

Fundamentals of Microfluidic Chips

Categories of Biochips. Biochips can be categorized into two groups: microarray and microfluidic chips. (Note that the term biochip is limited to meaning only microarrays in some literature). The microarray represented by a DNA chip or protein chip has an array of test sites that ranges from 10 to 500 microns in size typically. The number of test sites in a microarray varies from a hundred to a few thousand (Figure 1(a)), and microarrays for high throughput screening may have a million test sites on a coin-sized chip. In general, detection probes for the microarray are selectively addressed to the test sites by immobilization on the substrate of the microarray using covalent or noncovalent bonding. The types of probes include synthetic oligonucleotides, DNA/RNA fragments, enzymes, etc.[1] To detect target molecules and obtain desirable information, microarrays are typically scanned or imaged using fluorescence spectroscopy/microscopy or mass spectroscopy.

The microfluidic chip is often referred to as a "lab-on-a-chip" or μTAS (micro Total Analysis System),[4-6] since a microfluidic chip is supposed to incorporate the multiple functionalities of a typical biochemical analysis lab (Figure 1(b)). Unlike a microarray, the microfluidic chip consists of microchannels which connect these functionalities. Samples on a microfluidic chip are convected with fluids like buffer solutions through the microchannels while they go through the necessary processing steps such as mixing, reaction, separation, and detection. Since the sample flow is continuous on the chip, the analytic processes can be automated, minimizing sample contamination due to fewer human interactions and reducing the analysis time.

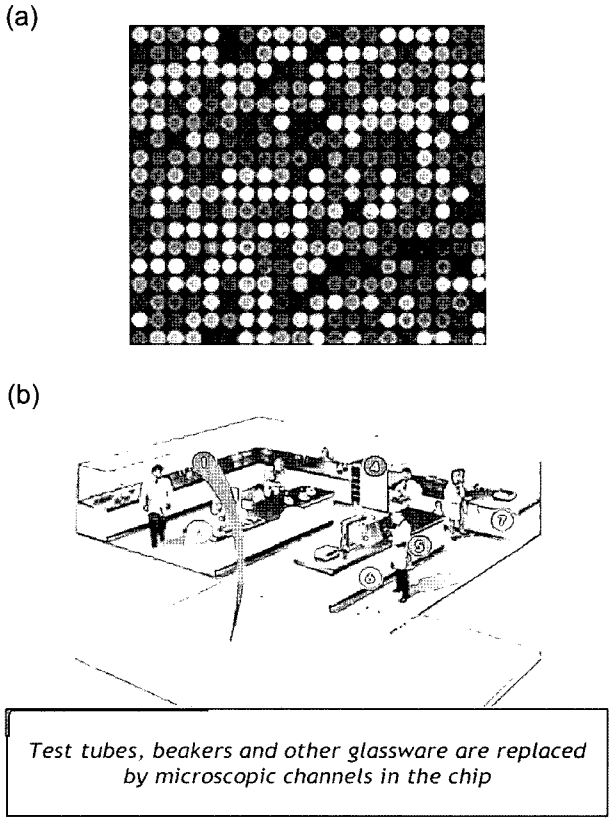

Figure 1. (a) Example of microarray and (b) cartoon of "lab on a chip" (courtesy of Caliper Life Sciences, Inc.).

General Features of Microfluidic Chips. The standard operations of a typical microfluidic chip include sample preparation, flow control, reaction/mixing, separation, and detection. On-chip sample preparation typically consists of sample purification procedures such as microdialysis[9-11] and sample preconcentration (Figure 2).[12] A biological sample solution should be extensively cleaned before analysis because an analyte of interest generally presents at a low concentration in a complex mixture. Also, the low concentration of the analyte requires sample preconcentration to help improve detectivity. Flow control is required when a sample plug needs to be injected into an analytical channel like a chromatography column and when samples are delivered from one site to another on a chip. Microvalves and micropumps have been extensively studied and developed for flow control in the past decade. Electrokinetic control using electroosmosis or electrophoresis and hydrodynamic control using a pressure gradient or surface tension are commonly used to control flows.[13]

To expedite chemical reactions of samples or change the

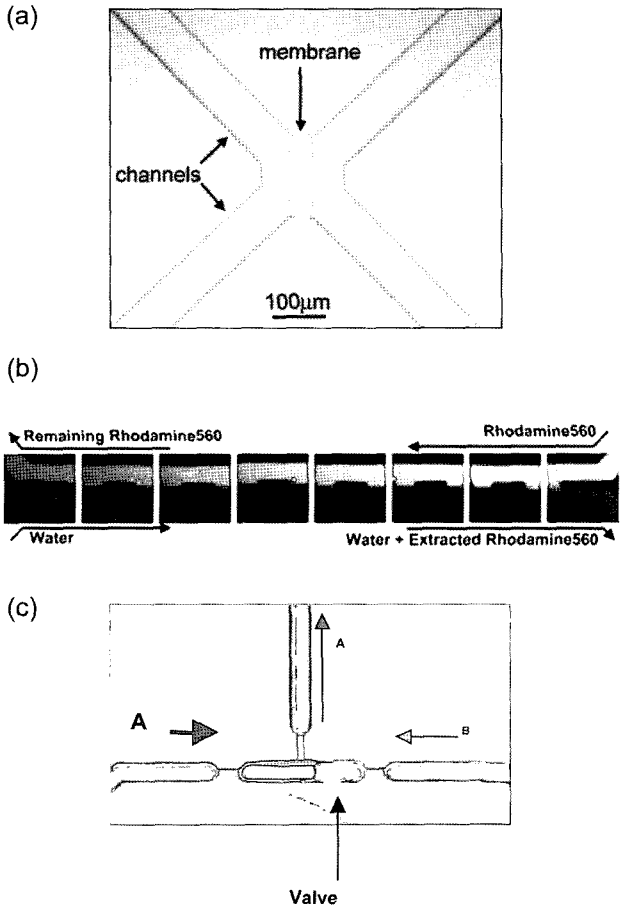

Figure 2. (a) Cross channel with laser-patterned porous polymer membrane used for sample preconcentration system (reprinted with permission from ref. 47, Copyright 2004 American Chemical Society). (b) Fluorescence dye extraction in a microdialysis system using a nanoporous polymer membrane (reprinted with permission from ref. 10, Copyright 2004 American Chemical Society). (c) Micro-check valve system using a polymer monolith (courtesy of Drs. D. Reichmuth, T. Shepodd, and B. Kirby).

component ratio of solvents, as in reverse phase chromatography or ion exchange chromatography, more than two sample streams should be mixed rapidly. Unfortunately, almost all flows on a microfluidic chip are laminar, meaning that fluid-mixing depends on molecular diffusion and that the mixing process is extremely slow, which may result in an unacceptably long microchannel. To enhance the mixing process, therefore, a microfluidic chip utilizes either a passive mixer that uses obstacles to cause chaotic mixing in a microchannel, or an active mixer that is operated with an external energy source to stir fluids by means of a microstirrer or ultrasonic wave.

Sample separation and clean-up is also a frequently required process on a microfluidic chip since biological samples generally consist of various components. For example, blood consists of both cellular (red and white blood cells) and non-cellular components (platelets, numerous proteins, nutrients, and ions). Even a protein sample solution purchased from a vendor is composed of not only protein, but many different ions in a buffer solution. When an unknown sample is analyzed, the target molecules or analytes should be separated from the other elements. Common on-chip separation techniques include chromatography, electrophoresis, and isoelectric focusing. Finally, various detection methods are used to detect or analyze the analytes of interest. A microfluidic chip can be connected to a mass spectroscope using a capillary or adaptor.[4-6] Optical detection using fluorescence or electrochemical detection using biosensors is also frequently used.

Fabrication of Microfluidic Chips. The typical fabrication technique used for microfluidic chips is soft lithography, including wet-etching, micro-contact printing, and hot embossing.[14] The substrate materials for microfluidic chips are glass or plastics such as PDMS and PMMA. Although the fabrication procedures depend on the material and complexity of a chip, for the sake of simplicity only a standard fabrication procedure for a 2-D glass microfluidic chip will be briefly discussed in this review. The basic procedure consists of photolithography, wet-etching and bonding (Figure 3).[3] The first step of the procedure is to deposit photoresist on the substrate surface. The photoresist surface is then exposed to UV radiation through a mask with an image of the microchannel pattern of the chip. After the substrate develops in an organic solvent, wet-etching is performed to transfer the pattern of microchannels to the substrate. The final step is the bonding of the substrate with a cover plate, following the removal of the photoresist layer. Two typical bonding techniques are anodic bonding and thermal bonding. The anodic bonding method uses electrostatic attraction and subsequent covalent bonding between the substrate and cover. The thermal bonding technique is commonly used, because it is efficient and easy to perform. However, it requires high temperatures (450-900 °C), which can damage immobilized

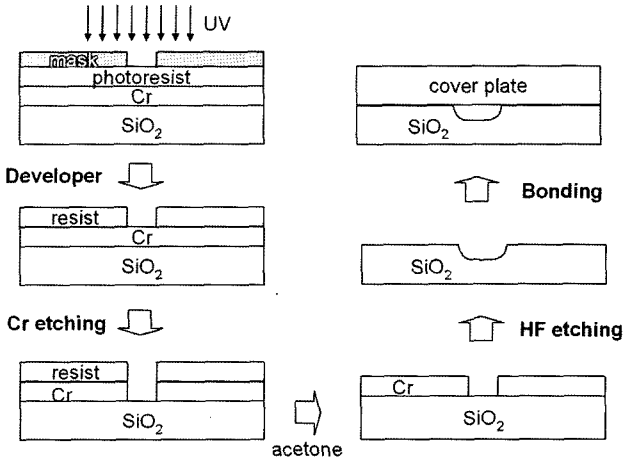

Figure 3. Schematic description of the fabrication process for microfluidic chips.

chemicals or materials used for various functionalities on the chip. Although low temperature bonding techniques have been recently developed, they are not yet universally applicable.

Applications of Microfluidic Chips. The applications of microfluidic chips include cell culturing or handling, clinical diagnosis, environmental monitoring, immunoassays, proteomics, DNA separation and analysis, polymerase chain reaction (PCR), and DNA sequencing. Since introducing specific examples is beyond the scope of this review, we only refer to several review articles for detailed applications.[4-6,8]

Essential Properties of Polymers for Microfluidic Chips

The control of the chemical and physical properties of organic polymers has been extensively investigated, which could allow the fabrication of controlled microstructures with various surface properties including hydrophobicity, conductivity, reflectability, roughness, oxidation state, and crystallinity.[15] Certain functionalities (e.g., carboxyl groups) of polymers can be generated during the fabrication process, and this has attractive potential applications for the polymers used in microfluidic chips.[16] The essential properties of a polymer useful for microfluidic applications include the hardness, surface charge, molecular adsorption, electroosmotic flow mobility, and optical properties,[17] which are important for both the fabrication process and successful application of the device. In this section, several essential properties that should be considered in selecting appropriate polymers for microfluidic chips are discussed.

Mechanical Properties. The glass transition temperature, a temperature where a polymer substrate changes from a rigid glassy material to a soft material, is very important for the fabrication of the polymer, and can usually be measured in terms of the stiffness (e.g. modulus). The melting temperature is the temperature at which a polymer flows, and is generally much higher than the glass transition temperature. The hardness of a material is also an important parameter in the fabrication process, and can be measured by indentation testing. Elasticity, the ability of a polymer to retain its original shape after deformation, is also important in the fabrication of microfluidic devices by soft lithography. Some basic properties of potential polymers for microfluidic applications are listed in Table I.[17-19]

Electrical Properties. It is critical that a polymer substrate exhibits good electrical insulating properties, so that the electric field will drop across the fluid-filled channel and not through the substrate in microfluidic systems. This effect can be evaluated by measuring the dielectric strength and electrical resistance of the polymer substrate. In contrast, electroosmotic flow (EOF) is generated by the surface charge on the microchannel walls in combination with an external electric field. The fabrication method, as well as the material itself, can affect the surface charge density and can significantly influence the EOF.[20,21] Branham *et al.* reported that imprinted PMMA channels could have highly charged walls, while hot embossed channels had a low surface charge density.[22] It was also reported that surface charge and EOF can be modulated using poly(ethylene terephthalate) glycol (PETG) by alkaline hydrolysis[23] and PDMS by plasma treatment.[24]

Thermal Properties. If heat is not effectively dissipated in microfluidic systems, elevated local temperatures can damage the microfluidic channels and significantly influence the efficiency of chemical separations. The thermal properties of polymers can be characterized by the thermal conductivity or thermal expansion coefficient of a polymeric material.

Table I. Various Properties of Polymers for Microfluidic Chips

	PMMA[a]	PC[b]	PETG[c]	LDPE[d]	PDMS[e]
Glass transition temperature (°C)	40 (isotactic)	150	81	-35	-130
Melting temperature (°C)	85–105	(230)	-	130	-
Tensile Modulus (GPa)	2.4–3.1	2.5	1.7	0.16–0.25	< 0.01
Hardness[f]	M80–100	R118/M74	R105	-	A20–60[g]
Coefficient of linear thermal expansion ($\times 10^6$ K^{-1})	50–90	68	91	100–220	10–19
Heat capacity (J/mol/K)	17–220	-	-	22-36	–
Dielectric constant[h]	2.8	2.9	3.2	2.2	3.0–3.5
Chemical resistance (weak acids)	Good	Poor	Fair	Excellent	Fair
Chemical resistance (weak bases)	Good	Poor	Fair	Excellent	Fair
Chemical resistance (alcohols)	Fair	Poor	Fair	Excellent	-
Chemical resistance (ketones)	Poor	Poor	Poor	Excellent	-

[a]PMMA, poly(methyl methacryate). [b]PC, polycarbonate (high viscosity). [c]PETG, poly(ethylene terephthalate) glycol. [d]LDPE, polyethylene (branched). [e]PDMS, poly(dimethyl siloxane). [f]Rockwell hardness number. [g]Shore hardness number. [h]Relative permittivity.

Surface Properties. Few approaches to chemically modifying the surfaces of polymers on microfluidic chips have been reported. An amino group was introduced to PMMA microfluidic channels that can be further derivatized to generate various functionalities.[25] Polyelectrolyte multilayer deposition and non-specific protein coating methods were also used to treat polymer microchannels for stable systems with a high surface charge density[23] and for biochemical assays,[26] respectively.

Forms of Polymers for Microfluidic Chips

Beads. Beads can be formed from many polymeric materials in a variety of ways with various useful functionalities.[27] Beads have been extensively used in analytical devices such as chromatography columns, and are basically used to increase the surface to volume ratio in the microchannels.[28] The size of frequently used beads for microfluidic chips is in the range of 5-50 μm in diameter. Beads should be kept within the channel and not flushed out when the device is in operation. For this purpose, the beads are trapped between frits within a chamber on the microfluidic device or immobilized on the surface. Andersson *et al.* demonstrated that a series of pillars could constrain beads placed in a microfluidic chip,[29] and this approach has been demonstrated to be useful in fabricating devices for single-nucleotide polymorphism analysis[30] and capillary electrochromatography (CEC).[31]

Beads can be modified to have various surface chemistries suitable for analytical operations. For example, antibodies (e.g., interferon-γ) were attached to beads and used for immunosorbent assays on a microchip.[32,33] A microfluidic chamber was packed with trypsin-immobilized beads and was used for on-chip protein digestion followed by electrophoretic separation in a separate channel.[34] A patterned array of beads formed on silica surfaces by a microcontact printing method was reported, which was useful for printing a protein such as biotin-labeled bovine serum albumin.[35] Functionalized beads have also been assembled on surfaces using hydrophobic/hydrophilic interactions[36] or assemblies of oligonucleotides.[37] In addition, beads were modified with temperature-sensitive poly(*N*-isopropylacrylamide) and placed in a channel at an elevated temperature.[38] The beads could then be released from the channel to be detected when the temperature is lowered.

Membranes. One form of polymeric supports frequently used as an alternative to beads in a microfluidic system is a membrane.[39] A poly(vinylidene fluoride) (PVDF) membrane was placed at the inlet of a channel on a microfluidic chip and used to desalt protein samples.[40] A miniaturized membrane reactor is constructed by fabricating the microfluidic channels on a PDMS substrate and coupling the microfluidics to a PVDF porous membrane that provided a large surface area for adsorption of trypsin, and this system was used to separate and detect various digested peptides.[41] Adsorbing a protein onto the membrane also allowed the system to be used for enantiomeric separations.[42]

A polycarbonate membrane was used to interconnect orthogonal channels, and was demonstrated to be useful for the detection of inorganic ions, bacteria, and enzymes.[43] A poly (tetrafluoroethylene) (PTFE) membrane was also used in microfluidic channels for electrokinetic trapping and the concentration of dilute solutions of DNA.[44]

A nitrocellulose membrane was fabricated on a glass substrate to apply the membrane within a microchannel.[45] In brief, after adsorbing an enzyme (e.g., trypsin) to the membrane, the substrate was manually assembled with a PDMS microchannel, and this system was used for an on-column enzyme reactor. Nylon monomers, one in an aqueous phase and the other in an organic phase, were introduced within a microfluidic channel and polymerized to form a membrane in a chip.[46] A two-phase system was recently reported to selectively photopolymerize 2-(*N*-3-sulfopropyl-*N*,*N*-dimethylammonium)ethyl methacrylate (SPE) in the presence of methylenebisacrylamide (BIS) using a focused laser, resulting in the formation of a membrane between support posts.[10] This approach was useful for *in-situ* fabricating dialysis membranes with both high and low molecular weight cutoffs. A similar membrane was also used to concentrate dilute proteins using electrophoresis.[47]

Gels. Gels have attracted much attention to date for analytical applications, including CEC.[48] However, their preparation in chips has been limited due to the difficulties of forming gels in microfluidic channels. A porous photopolymerized gel was placed in a separation channel of a borosilicate glass chip via UV irradiation of a mixture of 3-methacryloxypropyltrimethoxysilane, acid catalyst, porogen, and photoinitiator, and used for the separation of dyes.[49] Gels were also fabricated to preconcentrate analytes in a microfluidic channel because preconcentration is important in analyzing components found in low concentrations, as described earlier. Silica beads immobilized in a gel on a chip were demonstrated to be useful for the preconcentration of DNA samples as well as for further PCR amplification.[50]

It has also been shown that various proteins can be encapsulated within gels, including poly(ethylene glycol) (PEG) and polyacrylamide gels, on microchips for assays of biocatalytic activities. For example, proteins up to a molecular weight of 400,000 were immobilized in a polyacrylamide gel and used to study antigen–antibody interactions within the gel under electrophoretic flow.[51] The enzyme-incorporated gel on a PDMS chip was reported to be useful in producing an array of enzymatic reactors.[52] It was also demonstrated that multiple photopolymerized gel patches can be prepared within a channel, and each patch can be used as a pH sensor or can be prepared to analyze enzymatic activity (Figure 4).[53]

Gels have also been used for flow control due to the ability of a gel to swell or contract in response to environmental conditions.[54] Gels were fabricated in microfluidic channels

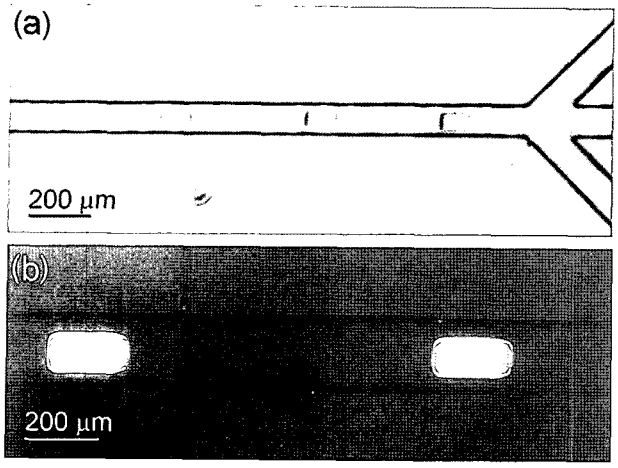

Figure 4. (a) Optical and (b) fluorescence micrographs of hydrogel micropatches prepared within a microfluidic channel (reprinted with permission from ref. 53, Copyright 2002 American Chemical Society).

by the photopolymerization of acrylic acid, 2-hydroxyethyl methacrylate, and ethylene glycol dimethacrylate in the presence of 2,2′-dimethoxy-2-phenyl acetophenone as a photoinitiator, and the gels were able to swell or contract depending on the pH changes of the surrounding medium.[55,56] These gels could form various geometries within the fluidic channel by photopatterning, and were demonstrated to be useful for forming valves within channels. Poly(*N*-isopropylacrylamide) gels were also placed and used to make valves in microfluidic channels by a photopolymerization method, resulting in the fabrication of a thermally responsive device in an aqueous phase.[57,58]

Recently, polymeric gel microparticles containing biocatalysts were prepared by *in situ* photopolymerization, which formed emulsions in pressure-driven flow in microchannels. This approach allows for the production of monodisperse particles, and their size can be controlled by the regulation of flow rates. In addition, both manufacturing microparticles and immobilizing biocatalysts can be performed simultaneously and continuously.[59]

Porous Polymer Monoliths. Monoliths were originally introduced to analytical chemistry as an alternative to standard bead-based HPLC columns, and porous monoliths can be easily formed by polymerization in the presence of a porogen.[60] Monoliths have been fabricated in specific areas of a microchip via photolithographic techniques based on UV-initiated polymerization methods.[61] A highly porous monolith was fabricated and demonstrated to be useful in the mixing of two fluorescent fluids on a chip.[62] Thermally responsive *N*-isopropylacrylamide was incorporated into the monolith and polymerized to fabricate a valve responding to temperature changes.[63] Rohr *et al.* recently introduced an *in situ* surface modification method by photografting acrylate or methacrylate onto the surface of the monolith using benzophenone, aimed at producing multiple functionalities within a single device.[64,65] Polymeric polystyrene-divinylbenzene monolithic nanocapillary columns were useful for the mass spectroscopic analysis of peptide mixtures. In contrast to the columns packed with microparticles, capillary columns were prepared in fused-silica capillaries by thermally induced *in situ* copolymerization of styrene and divinylbenzene, and a high level of sensitivity in the mass spectroscopic analysis was achieved.[66]

Fibers. Fibers are the most common curved objects with potential applications in microscale systems, and can be prepared by extrusion/casting,[67] layering,[68] and fugitive processes.[69] Jeong *et al.* reported a fabrication method to form microscale cylindrical polymeric structures (e.g., fibers, tubes) by employing 3-D multiple stream laminar flow and "on the fly" *in situ* photopolymerization (Figure 5).[70] A mixture of 4-hydroxybutyl acrylate, acrylic acid, ethyleneglycol dimethacrylate, and 2,2′-dimethoxy-2-phenyl-acetonephenone

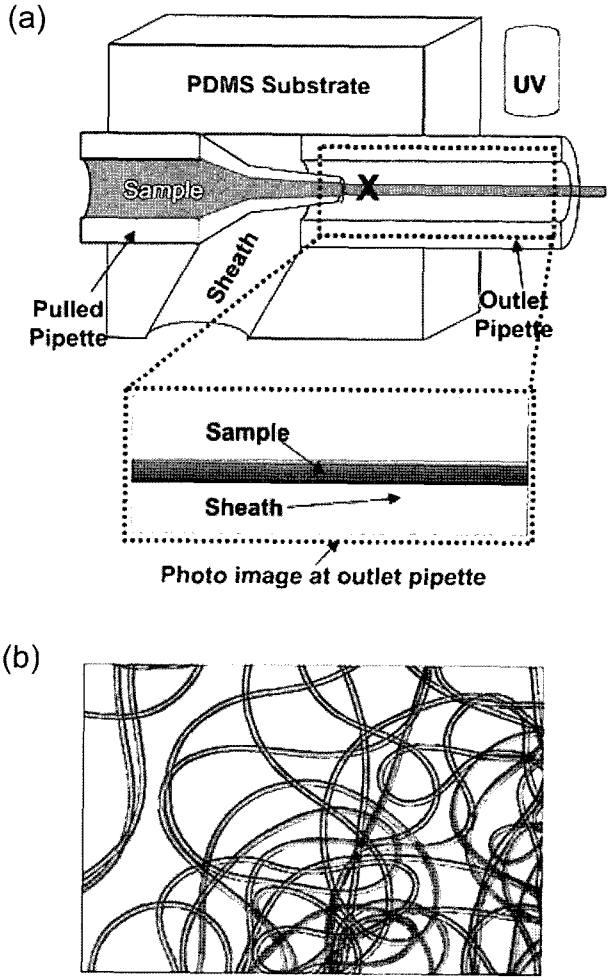

Figure 5. (a) Schematic description of the basic microfluidic apparatus for fabricating microfibers and (b) photomicrograph of the continuously produced microfiber (reproduced from ref. 70 by permission of The Royal Society of Chemistry).

was photopolymerized, and ethyl vinyl acetate tubes were used to form the fluidic networks that were designed to detect glucose as a biosensor.

Future Perspectives

We have summarized various properties and forms of polymers that are frequently used in microfluidic chips. Currently, the main limitations to using polymers in microfluidic systems include the difficulties of placing polymeric supports smaller than a few hundred microns in a microfluidic channel, although photopolymerization has been successfully used for the fabrication of solid polymeric supports. Laser-patterning polymerization allows membranes with a few microns of thickness, but it is generally difficult to overcome the issues of mass production for commercial uses. A variety of gels and monoliths have been synthesized and modified for use in a wide range of functional microfluidic systems. However, the difficulty in controlling the batch-to-batch reproducibility in the gel formation also suggests limited applications for the gels in microfluidic chips.

Polymers should meet certain criteria to be useful for microfluidic systems, and a critical future challenge of polymers facing this field is how polymers can be designed and modified to overcome the above-mentioned issues. Several design parameters of polymers for microfluidic chips can be derived from their essential properties, including the mechanical, electrical, thermal, and surface properties. In addition, incorporating various analytical or sensing functionalities into polymers is also important if polymers are to be widely used in the development of microfluidic chips. These design parameters of polymers can be manipulated and should be harmonized to design and fabricate microfluidic chips useful for biotechnology and life sciences.

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