Microfluid Nanofluid (2010) 9:145–161
DOI 10.1007/s10404-010-0605-4

REVIEW

Cyclic olefin polymers: emerging materials for lab-on-a-chip applications

Pedro S. Nunes · Pelle D. Ohlsson · Olga Ordeig · Jörg P. Kutter

Received: 20 January 2010 / Accepted: 9 March 2010 / Published online: 7 April 2010

Abstract Cyclic olefin polymers (COPs) are increasingly popular as substrate material for microfluidics. This is due to their promising properties, such as high chemical resistance, low water absorption, good optical transparency in the near UV range and ease of fabrication. COPs are commercially available from a range of manufacturers under various brand names (Apel, Arton, Topas, Zeonex and Zeonor). Some of these (Apel and Topas) are made from more than one kind of monomer and therefore also known as cyclic olefin copolymers (COCs). In order to structure these materials, a wide array of fabrication methods is available. Laser ablation and micromilling are direct structuring methods suitable for fast prototyping, whilst injection moulding, hot embossing and nanoimprint lithography are replication methods more appropriate for low-cost production. Using these fabrication methods, a multitude of chemical analysis techniques have already been implemented. These include microchip electrophoresis (MCE), chromatography, solid phase extraction (SPE), isoelectric focusing (IEF) and mass spectrometry (MS). Still much additional work is needed to characterise and utilise the full potential of COP materials. This is especially true within optofluidics, where COPs are still rarely used, despite their excellent optical properties. This review presents a detailed description of the properties of COPs, the available fabrication methods and several selected applications described in the literature.

Keywords Cyclic olefin polymers · Cyclo olefin copolymers · Microfluidics · Lab-on-a-chip

1 Introduction

Miniaturisation of chemical analysis systems employing microfluidic handling enables rapid and low cost analyses that generate little chemical waste (Becker and Gartner 2008). In the design of microfluidic systems, one must take into consideration, the type of material used to fabricate the device. The material has to be compatible with all the chemicals used, the temperatures applied, the biochemical and biophysical protocols and methods utilised, and the functional components involved in the miniaturised analysis. In the case of devices aimed for volume applications, the material should also be inexpensive and compatible with mass production microfabrication methods. Polymeric materials have been identified as a good alternative to conventional materials, such as glass and silicon, allowing to mass fabricate microsystems at affordable costs (Becker and Locascio 2002; Becker and Gartner 2008).

Selection of the most suitable polymer material is crucial for the fabrication approach as well as for the purpose of the chip. Some of the most common polymeric materials used to fabricate microfluidic devices are: poly(dimethylsilonxane) (PDMS) (Kee et al. 2008; Park et al. 2008b; Sia and Whitesides 2003), poly(methylmethacrylate) (PMMA) (Chen et al. 2008a; Tan et al. 2008), polycarbonate (PC) (Wang et al. 2005, 2008), polyester (Guo et al. 2005), polystyrene (PS) (Toft et al. 2008) and the negative photoresist SU-8 (Abgrall et al. 2007; Christensen et al. 2008;

Pedro S. Nunes, Pelle D. Ohlsson, and Olga Ordeig have equally contributed to this study.

P. S. Nunes (✉) · P. D. Ohlsson · O. Ordeig · J. P. Kutter
Department of Micro and Nanotechnology, Technical University of Denmark, DTU Nanotech, Building 345 East,
2800 Kongens Lyngby, Denmark
e-mail: pedro.nunes@nanotech.dtu.dk

Sikanen et al. 2007). Amongst these, SU-8 can easily be structured using standard lithography techniques, with features ranging from a few to hundreds of micrometers (Microchem 2009). Unfortunately, SU-8 has the drawbacks of high optical propagation losses in the UV region of the spectrum and high water permeability (Bilenberg et al. 2004; Mogensen et al. 2003). PDMS is probably the most popular polymer for soft lithography due to easy fabrication and bonding. It offers higher permeability to O_2 and CO_2 than any other polymer (facilitating cell culturing on chip), and it is optically transparent from the UV region to the NIR which is important for optical detection methods. However, its does not resist pressure above a few bars, swells in organic solvents, and surface treatments are often unstable over time (Mcdonald et al. 2000; Sia and Whitesides 2003). Rigid polymers, such as PMMA and PC, can be used to fabricate less deformable structures. However, their applicability is limited in some lab-on-a-chip applications due to their low stability against organic solvents. Organic solvents such as methanol and acetonitrile are, for instance, used to tune chromatographic separations.

Recently, a new group of polymers, cyclic olefin polymers (COPs), has been introduced as a promising plastic substrate for microfluidic devices. COPs, in contrast to other polymers used for lab-on-a-chip applications, are highly resistant to chemicals including polar solvents (Topas Advanced Polymers 2009; Zeon Chemicals 2009). The high chemical resistance is opening the door, for the first time, to use polymeric microfluidic systems, e.g. in organic electrochemistry applications. COPs also present a high biological inertness that makes them suitable for biomedical applications (Bhattacharyya and Klapperich 2006; Choi et al. 2009), allow long-term stable surface treatments (Huang et al. 2000; Hwang et al. 2008; Steffen et al. 2007), and provide a low water absorption (Japan Synthetic Rubber 2009; Mitsui Chemicals America 2009; Topas Advanced Polymers 2009; Zeon Chemicals 2009). Low water absorption is beneficial to ensure that the dimensions of the structures do not change with the environmental conditions. Moreover, COPs are highly transparent in the visible and near ultraviolet regions of the spectrum making the polymer also very interesting for optical components (Hansen et al. 2005).

The aim of this article is to provide the reader with a review of the current state-of-the-art regarding the use of COPs for microfluidic applications. First of all, we describe the physical and chemical properties of the polymer, which are indisputably the reason for its increasing popularity. This is followed by a description of the methods available to fabricate COP devices, and a summary of the different applications of COP microfluidic systems found in the literature. Finally, we draw some conclusions and point out future possibilities for this family of materials.

2 Chemical and physical properties of COPs

In this section, we present the chemical and physical properties of the COPs, putting special emphasis on comparing the properties of the COPs with other common polymers used for lab-on-a-chip applications. Many of the properties are summarised in graphs and tables to simplify the selection of the most suitable material for various applications.

Cyclic olefin polymers are a class of polymers based on cyclic olefin monomers and ethene. Different COP materials are commercially available under various brand names: TOPAS by Topas Advanced Polymers GmbH (2009), APEL by Mitsui Chemicals America Inc. (2009), ARTON by Japan Synthetic Rubber Co. (2009) and Zeonex and Zeonor by Zeon Chemical L.P. (2009). Slightly different materials are obtained depending on the cyclic monomer and the polymerisation process used for their synthesis (Shin et al. 2005). Two different polymerisation processes are used, chain copolymerisation of cyclic monomers with ethene (Topas and Apel), and ring-opening metathesis polymerisation of cyclic monomers followed by hydrogenation (Arton, Zeonex and Zeonor), as shown in Fig. 1. Since the former polymers are made from more than one type of monomer, they are usually referred to as cyclic olefin copolymers (COCs), whilst the latter are usually called COPs. Both COP and COC are often used as general terms for the whole group. In this article, we have chosen to use COP as the collective term, since some of the polymers are not copolymers.

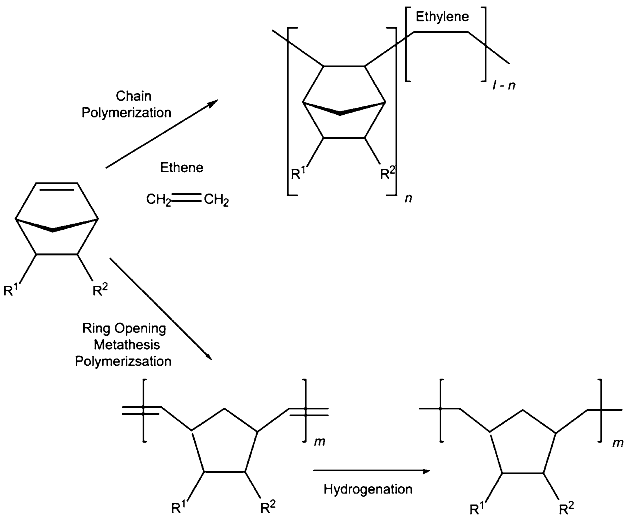

Fig. 1 Typical polymerisation schemes and generalised chemical structures for COPs (Shin et al. 2005) starting from a generic norbornene

2.1 Chemical properties

Cyclic olefin polymers (COPs) have a low water absorption (<0.01%), four times less than PC and 10 times less than PMMA, even in high humidity environments (Japan Synthetic Rubber 2009; Mitsui Chemicals America 2009; Topas Advanced Polymers 2009; Zeon Chemicals 2009). Low water absorption provides excellent dimensional stability in changing environmental conditions, which is beneficial when the polymer is used for, e.g. optical purposes, since it provides a stable focal length (Appasamy et al. 2005).

The hydrophobicity of the COPs can be problematic in microfluidic devices (water contact angles around 90°, see Table 1). In order to decrease the surface hydrophobicity low-pressure plasma (Nikolova et al. 2004), oxygen plasma (Hwang et al. 2008), UV/ozone (Tsao et al. 2007) and chemical coating treatments (Stachowiak et al. 2007; Steigert et al. 2007; Tsao et al. 2007; Zhang et al. 2008) have been investigated. The results are summarised in Table 1.

Sometimes, hydrophobic patches are useful (e.g. to control liquid flow). Hydrophobicity can then be increased locally by ‘writing’ fluoropolymers onto the channels with a flit pen (Steigert et al. 2007).

In addition to the low water absorption, COPs are resistant to hydrolysis, by acids and alkaline agents, as well as to polar solvents, such as methanol. However, the material is attacked by non-polar organic solvents, such as toluene and hexane. Table 2 compares the chemical resistance of COP with other common polymers used in microfluidic applications.

Table 2 Qualitative chemical resistance comparison between COPs and other common polymer substrates used in microfluidics

	COP	PMMA	PC	PS
Acids, dilute or weak	+	°	+	+
Acids, strong and conc.	+	–	–	°
Alcohols, aliphatic	+	–	°	+
Aldehydes	°	°	°	–
Bases	+	°	–	+
Esters	+	–	–	–
Hydrocarbons, aliphatic	–	°	°	–
Hydrocarbons, aromatic	–	–	–	–
Ketones	°	–	–	–

Here, (+) signifies resistance, (°) limited resistance (swells), and (–) no resistance (dissolves). The data is from Topas Advanced Polymers (2009) for COP and Ace Glass (2010) for the other polymers

2.2 Physical properties

2.2.1 *Optical properties*

Cyclic olefin polymers (COPs) have been identified as interesting materials for optical applications. Hwang and Yu (2005) and Nilsson et al. (2005) exploited COP as a waveguide core material. Appasamy et al. (2005) used COP, for the first time, for microlens applications, and Hansen et al. (2005) presented a COP lab-on-a-chip system, which integrates microfluidics and optics. These applications have been possible due to the fact that COPs have a high optical transparency over a wide wavelength range (from 300 to 1200 nm; Topas Advanced Polymers 2009; Zeon Chemicals 2009), a high refractive index (1.53 for Topas 5013; Khanarian and Celanese 2001), a large Abbé number (56.4 for Topas 5013; Khanarian and Celanese 2001) and a low birefringence. Moreover, in the near UV region, the transmittance is higher than for other polymers, such as PMMA, PC and PS. The transmission spectrum varies slightly in the region between 200 and 300 nm for different brands and grades, but an example is shown in Fig. 2.

Another crucial property is the autofluorescence of a material, which should be low when fluorescence detection is employed. The autofluorescence of COPs is higher than for Borofloat glass and PDMS, but in the same order of

Table 1 Surface treatments to reduce hydrophobicity of COP materials

Surface treatment	COP material	Water contact angle		Reference
		Native material	Treated material[a]	
Low-pressure plasma	Topas 6017	91°	39°	Nikolova et al. (2004)
Oxygen plasma	APEX	90°	7°	Hwang et al. (2008)
UV/ozone	Zeonor 1020 R	95°	49°	Tsao et al. (2007)
Photografting of PEGMA	Topas 8007 × 10	88°	45°	Stachowiak et al. (2007)
Photografting of PEtOx	Topas 5013	95°	50°	Steigert et al. (2007)
Permanent PVA coating	Zeonor 1020 R	95°	74°	Tsao et al. (2007)
Dynamic HEC coating	Topas 8007	90°	57°	Zhang et al. (2008)

[a] The reported contact angle for the treated material is the smallest one achieved

PEGMA poly(ethylene glycol methylacrylate), *PEtOx* polyhydroxyethyloxazoline, *PVA* polyvinyl alcohol, *HEC* hydroxyethyl cellulose

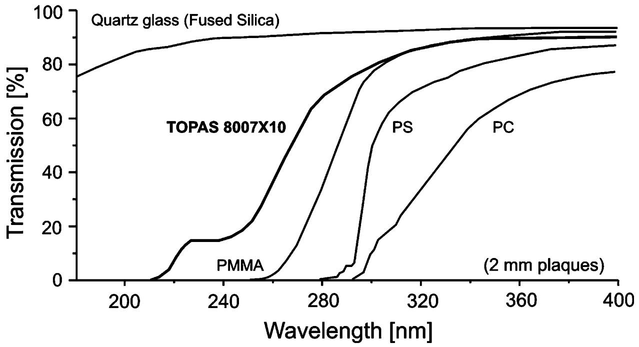

Fig. 2 Transmission comparison between Topas 8007X10, other common polymer substrates and quartz glass used in microfluidics for wavelengths ranging from 200 to 400 nm (Topas Advanced Polymers 2009)

magnitude as for PMMA and PC (Piruska et al. 2005). It is lower for longer wavelengths and decays with illumination time. According to Hawkins and Yager (2003), it also varies between different brands of COP, with a higher observed autofluorescence for Zeonor than for Topas.

In Table 3, the optical properties of COPs are compared to those of PC and PMMA.

2.2.2 *Thermal properties*

Cyclic olefin polymers are commercially available in different grades with different glass transition temperatures (T_g). Figure 3 compares the T_g for different commercialised COPs with other common polymers used in microfluidics. Notice that T_g increases with a higher cyclic olefin content and that there are COP grades with a higher glass transition temperature than PMMA, PC and PS (Shin et al. 2005). For example, Topas is available in grades with glass transition temperatures ranging from 33 to 180°C by changing the content of the norbornene component (a cyclohexene ring bridged with a methylene group in the para position, see Fig. 1) (Topas Advanced Polymers 2009). This makes it possible to use COPs in applications exposed to higher temperatures without the risk of deformation.

On the other hand, COPs show a distinct softening at their respective T_g. As will be discussed in the fabrication section, this particular property of thermoplastic materials is used for thermal bonding processes, e.g. to fabricate structures in high T_g COP grades using replication methods and then seal the imprinted structures with a low T_g COP grade (Bilenberg et al. 2005; Nielsen et al. 2004) in the bonding step.

2.2.3 *Mechanical properties*

Cyclic olefin polymers (COPs) are thermoplastics with high strength and rigidity. Their mechanical properties vary between brands and grades, but are generally similar to those of PC and PMMA. The different properties are summarised in Table 3.

Table 3 Comparison of the general physical and optical properties of different brands of COP with other clear polymers

Property	TOPAS (Topas Advanced Polymers 2009)	ZEONEX (Zeon Chemicals 2009)	APEL (Mitsui Chemicals America 2009)	ARTON (Japan Synthetic Rubber 2009)	PC (Lamonte and Mcnally 2001)	PMMA (Lamonte and Mcnally 2001)
General						
Density (g/cm^3)	1.02	0.95–1.01[a]	1.02–1.04[a]	1.08	1.2	1.2
Flexural modulus (MPa)	3450	1600–3100[a]	2400–3200[a]	2650–3300[a]	2340	3100
Tensile strength (MPa)[b]	46–63[a]	45–71[a]	50–60[a]	52–78[a]	62	69
Ball indentation hardness H961/30 (N/mm^2)	130–190[a]	–	–	125	175	110
Water absorption (%)	<0.01	<0.01	< 0.01	0.2–0.4[a]	0.04	0.1
Optical						
Transmission (%)	92	0–92[a]	92	93	88	92
Haze (%)	<1	<0.1	< 1	0.6	1	1
Index of refraction	1.53	1.509–1.535[a]	1.53	1.512–1.523[a]	1.586	1.491
Abbé number	58	55.7–56.2[a]	58	57	34	61
Birefringence	Low	Low	Low	Low	Variable	Low
Stress-optical coef. (10^{12} Pa/s)	4	–	–	–	68	−4.6

– no data is available

[a] The property value varies within the range of values provided depending on the COP grade

[b] The tensile strength values should be seen as approximate values, since the measurement protocol used was not always specified

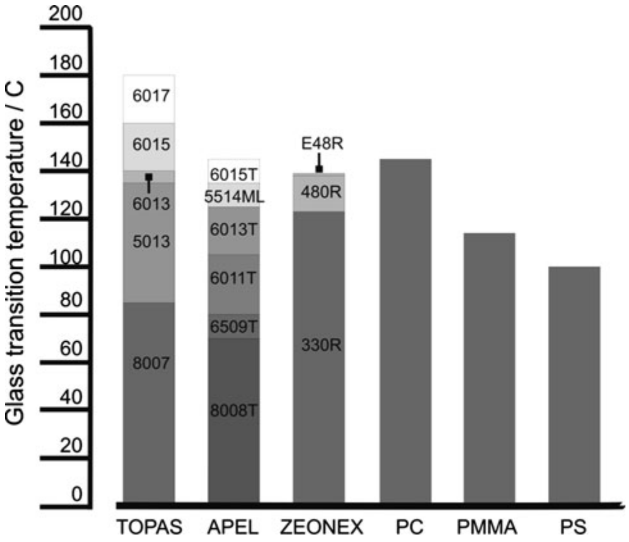

Fig. 3 Glass transition temperatures of different COPs compared to other standard polymers used in microfluidics: polycarbonate (PC), poly(methylmethacrylate) (PMMA) and polystyrene (PS). The glass transition temperatures for the different grades of COPs are according to the fabricant specifications (Mitsui Chemicals America 2009; Topas Advanced Polymers 2009; Zeon Chemicals 2009)

2.2.4 *Electrical properties*

The electrical properties of the substrate material are especially interesting for electromigration and electroseparation applications, where a high voltage should be applied without causing dielectric breakdown through the substrate. COPs have very good electrically insulating properties, with a volume resistivity above 10^{16} Ω cm, and a dielectric breakdown voltage of 30 kV/mm (Lamonte and Mcnally 2001), as well as a dissipation factor below those of polystyrene (PS) and polypropylene (PP) (Lamonte and Mcnally 2001). The room temperature dielectric constant of COPs is about 2.35, and it is less dependent on temperature than the dielectric constants of polypropylene (PP) and other olefinic materials (Topas Advanced Polymers 2009).

2.3 Biological inertness

The substrate material of a microfluidic chip can have significant effects on the performance of biological assays. It can, for instance, affect adhesion, growth and behaviour of cells, cause adsorption of DNA and proteins, or denature proteins. These effects are important to consider when choosing a substrate material for biological applications.

Cyclic olefin polymer (COP) chips have been successfully used for analysis of several kinds of biological samples, such as blood (Choi et al. 2009; Grumann et al. 2006; Jang et al. 2006) and DNA (Bhattacharyya and Klapperich 2006; Gulliksen et al. 2005; Larsen et al. 2008). In order to reduce protein adsorption, Stachowiak et al. (2007) photografted poly(ethylene glycol) methylacrylate (PEGMA) in Topas channels. This reduced the adsorption of fluorescein-labelled bovine serum albumin (FL-BSA) by 78%. Zhang et al. (2008) used a dynamic coating of hydroxyethyl cellulose (HEC) for the same purpose, reducing the FL-BSA adsorption to an undetectable level.

Johansson et al. (2002) investigated cell growth on Topas (5513X2), Zeonex (480R), PMMA, PS and SAN (styrene–acrylonitrile copolymer). They compared cell number, spread and morphology of HeLa cervix carcinoma cells on untreated and air plasma-treated substrates to commercial tissue-culture PS. None of the untreated substrates were suitable for culturing these cells, but Zeonex, PS and SAN substrates with the right air plasma treatment were as good as the commercial substrates. This was not achieved for Topas and PMMA. The difference between Topas and Zeonex is possibly due to additives in the polymers.

Since the effect on biological molecules might vary between different brands and grades of COP, it is a good strategy to investigate this and possible surface modifications in the literature or experimentally for the intended application before choosing a substrate material.

3 Fabrication methods

This section describes the available fabrication and bonding methods for COPs. Recently, a considerable emphasis has been put on the fabrication of several COP devices by replication techniques, such as hot embossing, injection moulding and nanoimprint lithography (NIL) (Bilenberg et al. 2005; Kameoka et al. 2001; Steigert et al. 2007). These methods are efficient for low-cost production; however, they are not the most adequate methods for fast prototyping. Hot embossing and NIL can be used to produce a small number of complex structures, whereas injection moulding is more suitable for large-scale fabrication. Direct structuring methods, such as micromilling and laser ablation, are more time consuming (depending on the time taken to fabricate a single device), but perfectly suitable for COP fast prototyping (Bundgaard et al. 2006; Steigert et al. 2007).

The choice of COP type and grade is closely related to the fabrication method. COP can be purchased either in pellet form (e.g. for injection moulding), in solution (e.g. for nanoimprinting), or in sheets (e.g. for hot embossing). Pellets may require to be dissolved in a proper nonpolar solvent, such as toluene or *sec*-butyl benzene, except if injection moulding is used.

3.1 Replication methods

3.1.1 Injection moulding

Injection moulding is one of the most common techniques for the fabrication of macroscopic polymer parts, since it offers short fabrication cycle times (Rotting et al. 2002). The fabrication process consists of two major steps: mould fabrication (needed for each new design) and injection moulding (Attia et al. 2009). The high temperature and pressure ranges used when moulding, limits the use of silicon (Si), resists and other polymers as mould material, thus metals are commonly chosen (Kim et al. 2006). The mould inserts are typically fabricated by standard photolithography techniques [for instance, using SU-8 (Kim et al. 2006) or AZ4620 resist (Appasamy et al. 2005)], followed by electroplating (Chen et al. 2008b; Choi et al. 2009; Mccormick et al. 1997; Mela et al. 2005).

In injection moulding, pellets of COP are fed to the hopper of the injection moulding machine. The material is transported in the mould direction and simultaneously melted at a high temperature. The polymer is then injected with high pressure against the mould, which is kept at the de-moulding temperature. The injection lasts for a very short time, after which a constant packing pressure is applied to the COP. The sample is then cooled down and demoulded. There are many parameters in the injection moulding process that have a direct effect on the COP replicas. For example, Ito et al. (2007) analysed how the injection speed, mould wall temperature and structure depth affect the COP replicas. Furthermore, Ito et al. showed that the injection moulded part has a structure distribution within itself, made of a skin–shear–core structure with different molecular orientations. Hence, surface replication properties are not only influenced by the pressure distribution inside the mould but also by the internal structural development (Ito et al. 2007). Angelov and Coulter (2008) developed COP gratings using two different injection moulding conditions showing that higher temperatures in various parts of the injection moulding machine (e.g. nozzle and mould) lead to better quality replicas. Higher temperatures typically lead to a better flow behaviour, thus to a better filling of the master cavities. Monkkonen et al. (2002) and Kalima et al. (2007) compared the filling properties of COP during injection moulding with other polymers. 600 nm wide and 200 nm deep lines were nicely filled by the different polymers analysed; however, the 100 nm wide and 200 nm deep structures were better filled by polycarbonate than by COP (Monkkonen et al. 2002). Despite that, Appasamy et al. (2005) injection moulded microlenses in COP. Here, it was claimed that apart from the favourable optical properties, COP also had excellent flow behaviour for injection moulding.

In injection moulding, as in several other replication methods, the quality of the replicated structures depends to a great extent on the master, which typically is metallic, and intrinsically on its fabrication process. A nickel mould has been used by Choi et al. (2009) to replicate low aspect ratio structures in Topas (grade 5013, Topas Advanced Polymers GmbH). Here, a high pressure of 70 MPa and a melt temperature of 280°C have been used. Kim et al. (2006) have also used an electroplated nickel mould to sustain a pressure of 30 MPa and a melt temperature of 290°C, whilst injection moulding pillars with a minimum width of 50 µm in a 1.5 cm long and 1 cm wide channel in Topas (grade 5013, Topas Advanced Polymers GmbH). Steigert et al. (2007) have succeeded in circumventing the need of a time consuming metallic master fabrication process by using a high-performance epoxy containing aluminium powder as a master. Steigert and coworkers reported that no master degradation after 200 cycles occurred when injection moulding channels in COP discs, but without specifying either the used pressure or temperature.

Standard photolithography and etching procedures can be done on a COP wafer, due to the high chemical resistance of COP. The possibility of performing standard photolithography and etching procedures is rather attractive, since the fabricated devices can, for instance, have integrated temperature sensors, thus diversifying the number of lab-on-a-chip applications. Standard photolithography and etching procedures are already used in the semiconductor industry for mass fabrication of several devices, thus a process combining injection moulding and the referred techniques would be beneficial for the fabrication of lab-on-a-chip devices. The main shortcoming of such a combined process would be the increased fabrication time, when compared to typical times for injection moulding fabricated devices. Lee et al. exploited this fact to wet etch gold using an aqueous solution of potassium iodide and iodine $(KI \cdot I_2)$ on a low roughness flat COP wafer prepared by injection moulding using highly polished electroplated moulds. The etched gold patterns were used to fabricate microheaters, temperature sensors and microelectrodes, where the thermal stability of COP was another inherent advantage (Lee et al. 2005).

In the experiments, performed by Lee et al. (2005), it was noticed that the gold adhesion to the COP substrate was better than when using a typical pre-adhesive layer (usually Cr or Ti). The lack of an adhesion layer is an advantage especially when fabricating microelectrodes, since it eliminates the need of a passivation layer to protect the edges of the electrode that expose the adhesion layer to the solution. Angelov and Coulter (2008) similarly demonstrated the good adhesion between COP and metals, in this case, 150–250 nm thick Al. No pre-adhesive layer was used and delamination did not occur upon substrate immersion in deionised boiling water. Photoelastic tests were also performed and high stress levels were only observed around specific moulded parts, demonstrating the suitability of COP for optical applications (Angelov and Coulter 2008).

Most of the study reported so far consists in the fabrication of rather large structures (e.g. $100 \times 60\ \mu m^2$ microfluidic channels). However, replication of nanostructures into polymer surfaces has also received considerable attention, where the fabrication of biomedical materials is one of its several possible applications. Gadegaard et al. (2003) successfully replicated in Topas (grade 8007, Topas Advanced Polymers GmbH) collagen fibrils with 30 nm groove widths and depths up to 5 nm, where the nanotopography is assumed to influence cellular behaviour. So far, the main limitation seems to lie in the grain size of the master material, to successfully replicate even smaller structures.

3.1.2 Hot embossing

In hot embossing, the material is in wafer or sheet form (Mela et al. 2005; Tsao et al. 2008; Yang et al. 2005a). This was achieved by some groups by melting COP pellets at 140°C in a mould under a pressure of 10 MPa for 1 min (Faure et al. 2008). However, such sheets can also be acquired commercially, for instance, from Zeon Chemical L.P. (2009).

In hot embossing, a microstructured mould is pressed against a COP sheet or wafer heated above the glass transition temperature. Depending on the master material, design and type of COP to be embossed different process parameters have to be optimised. The applied pressure, time and temperature are the most important factors influencing the end quality of the embossed structures in the chip. Parameter variation during hot embossing of COP (e.g. compression rate, moulding temperature and pressure) has been extensively investigated in terms of the resulting device properties by Fredrickson et al. (2006). Channel depth was observed to be independent of the compression rate, moulding temperature and compression force in the analysed ranges. Furthermore, Fredrickson et al. (2006) showed that lower mould temperatures and cooling rates led to smaller areas with visible stress whitening.

Hot embossing is generally done using lower pressure and temperature ranges than injection moulding. Despite the typically low pressure and temperature used (0.5 MPa and 125°C), Faure et al. (2008) used a nickel/stainless steel mould to emboss fluidic channels into Zeonor (grade 1020R, Zeon Chemicals). A constant pressure of 0.5 MPa was applied for 10 min to the heated material and also whilst it cooled down to 80° C. A steel master has been used by Dhouib et al. (2009) to hot emboss Topas (grade 5013, Topas Advanced Polymers GmbH). A steel substrate was laser machined and pressed against the heated Topas ($T_g + 50°C$) with a pressure of 2.5 MPa over a $40^2\ mm^2$ square for an unspecified amount of time. De-moulding was performed at $T_g - 50°C$ and even though no anti-sticking layer (to prevent the polymer from sticking to the stamp and facilitate its release) was used a good fidelity was achieved for the rather large embossed structures (~100 μm wide channels). Similar pressure and temperatures were used by other groups with Si masters (Park et al. 2008b; Yang et al. 2005a). Kameoka et al. (2001) cut Zeonor polymer sheets into the size of the final chips before embossing them using a silicon master. The embossing occurred at 130°C and with a pressure of 1.7 MPa applied for 7 min. After embossing, the master and the substrate were cooled down to a temperature below the glass transition temperature and then de-moulded. In this way, Kameoka et al. (2001) embossed capillary electrophoresis chips in Zeonor (grade 1020, Zeon Chemicals) polymer sheets obtaining 60 μm wide and 20 μm high channels, with smooth surfaces.

SU-8 has also been used as a master material for embossing COP under conditions similar to the ones used with Si masters; however, these masters could typically only be used <10 times (Liu et al. 2007). SU-8 masters have also been used by Bhattacharyya and Klapperich (2006) to emboss Zeonor; however, in this case, an aluminium coating was used to facilitate the substrate separation from the master. Illa et al. (2009) used an anti-sticking layer on their Si master to facilitate the release of the 15.3 μm wide cylindrical pillars in a pillar array embossed in Zeonor (ZeonorFilm, ZF 14-188, Zeon Chemicals). In hot embossing, the distance of the COP has to flow towards the master is considerably smaller than in injection moulding, which may lead to reduced stress and shrinkage effects (Gerlach et al. 2002). Hence, more fragile structures with higher aspect ratios than the ones achieved with injection moulding are feasible. High aspect ratio structures, 200 nm wide and 60 μm high, have been fabricated in COP by Yoo et al. (2009) using an anodic aluminium oxidation nanostructured membrane. This membrane was later dissolved to release the embossed nanostructures. Monkkonen et al. (2000) embossed 125 nm deep cylindrical pillars with a radius of 150 nm, to be used as an antireflecting element, in Topas. Scanning electron microscopy and optical transmission characterisation showed that the initial master structure was well-replicated.

3.1.3 Nanoimprint lithography

Nanoimprint lithography (NIL) can be used to fabricate COP structures with minimum features in the nanometer range. Lab-on-a-chip systems fabricated by hot embossing are typically made using a thick polymer substrate. In hot embossing, only a small portion of the substrate is embossed compared to the initial substrate thickness. In NIL, either the entire or nearly the entire thickness of the polymer film is patterned, leading to a thin or non-existent residual layer. The advantage of a thin residual layer lies in the possibility of integrating optical components on Lab-on-a-chip devices. Moreover, in nanoimprinting, the high degree of control of the temperature and pressure distribution enables the fabrication of sub-micrometer structures at sub-wavelength resolution.

Nanoimprint lithography (NIL) requires the COP material to be spun onto a substrate that can be silicon, silicon dioxide (Bilenberg et al. 2005) or glass wafers (Gustafsson et al. 2008). COP can be commercially acquired in solution (e.g. from (Topas Advanced Polymers 2009)) or in pellet form. If pellets are used, these need to be dissolved in a proper nonpolar solvent, such as toluene or *sec*-butyl benzene. A substrate material with a lower refractive index than that of COP (oxidised silicon or glass wafers) enables the fabrication of waveguides and other optical components, thus taking advantage of the high optical transmission of COP materials (Hwang and Yu 2005).

A good adhesion and a homogenous distribution of the COP film on the substrate are assured by pre-cleaning the wafers in a solution of sulphuric acid and hydrogen peroxide (4:1 (v/v)), to remove any native oxide layer and organic impurities, and dehydrating. The substrates are baked after spin-coating to remove the solvent in which the COP was diluted. A higher temperature than the glass transition temperature of the polymer, but lower than the evaporation point of the solvent (e.g. 110°C for toluene and 174°C for *sec*-butyl) should be used to prevent bubble formation in the film upon baking.

The quality of the imprinted replica structure depends again to a great extent, like in other replication methods, on the master used. In this case, due to the low pressures used (0.2–1.9 MPa; Nilsson et al. 2005; Hansen et al. 2005) and the fairly moderate temperatures (c.a. 190°C), silicon is the preferred master material (Nilsson et al. 2005). The master consists of a negative pattern of the chip layout. These are usually fabricated on 4 inch wafers, with the possibility of being scaled up (Gourgon et al. 2005). The pattern from the mask is transferred to the wafer using UV photolithography or electron beam lithography for smaller structures. Deep-reactive ion etching (DRIE) is then used to transfer the resist pattern into the silicon wafer. The resist is then stripped off either in an O_2 plasma or in acetone. Negatively sloped sidewalls and high sidewall roughness are undesirable. These may cause the imprinted structures to remain 'trapped' inside the cavities of the master (Gustafsson et al. 2008). Sidewall roughness can be further decreased after processing by thermally oxidising the silicon stamp (Nielsen et al. 2004; Nilsson et al. 2005). Finally, to prevent the polymer from sticking to the stamp and facilitate its release, the use of an anti-sticking layer is recommended. A layer of (1*H*,1*H*,2*H*,2*H*-perfluorodecyltrichlorosilane) deposited by chemical vapour deposition has been successfully used by Gustafsson et al. (2008) for this purpose.

Imprinting is done in a vacuum chamber with two parallel plates that can be pressed together. First, the sample is heated-up above the glass transition temperature (usually 90°C above T_g; Bilenberg et al. 2005; Nilsson et al. 2005). Then, the stamp is pressed against the substrate at a pressure ranging from 0.2 to 1.9 MPa, for a period of time raging from 5 to 10 min. After the imprinting step, the sample is cooled down to a temperature lower than T_g, whilst the pressure is maintained to avoid deformations. Finally, the stamp and substrate are separated at room temperature.

In most NIL processes, there is a residual polymer layer after imprinting the substrate. Removal of this residual layer is crucial in waveguiding structures. An O_2 plasma in a standard reactive ion etcher system can be used to etch the remains of the residual layer (Bilenberg et al. 2005; Hansen et al. 2005). The etching process should be done with care, since it also heats the sample, thereby causing polymer reflow (Hansen et al. 2005). So far, the smallest structures imprinted in a 7 μm thick COP film, spun on 4 inch silicon wafer, are presented in Fig. 4 (Gustafsson et al. 2008). These structures are part of an electrochromatographic column, where the distance between the 4.4 μm wide and 4.9 μm high pillars is 1.6 μm.

3.1.4 *Other methods*

Soft lithography is a technique used for fabricating structures using elastomeric materials (e.g. PDMS). Steigert et al. (2007) used a PDMS master to emboss channels in Topas discs (grade 5013, Topas Advanced Polymers GmbH). The PDMS master was cast on a negative SU-8 master. The PDMS properties were chosen as a compromise between a low viscosity to promote a good filling of the primary SU-8 master cavities and a low deformability, to withstand an applied force of 3 kN for 5 min at 175°C when embossing the Topas discs.

Mosaddegh and Angstadt (2008) described a technique based on replicating structures in Topas (grade 6013, Topas Advanced Polymers GmbH) by heating the mould to 241°C, without applying any force other than gravity, thus avoiding the use of expensive fabrication machinery (e.g. a hot embossing system). Here, the authors illustrated the importance of interfacial effects and viscosity in filling and replicating microstructures. A hollow metal cylinder is placed over the structured mould surface, and then filled

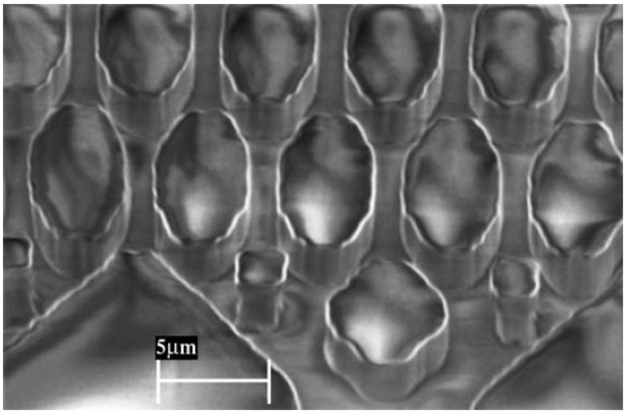

Fig. 4 SEM image of pillar structures of an imprinted chromatography column in Topas. The 4.4 µm wide pillars, separated by a gap of 1.6 µm, were used directly as the stationary phase (Gustafsson et al. 2008)

with pellets. The mould and the hollow cylinder filled with pellets are heated to the desired temperature and after 5 min of moulding; the stack is brought to room temperature for 10 min and then de-moulded, where the features are replicated on the lower base of the cylinder. The aspect ratio of the fabricated COP structures was not as good as for PS and PMMA, due to sticking to the silicon oxide stamp (Mosaddegh and Angstadt 2008). This drawback could probably be avoided if an anti-sticking layer had been used (Gustafsson et al. 2008). The long process time ($\sim$45 min), when compared to injection moulding, makes this replication method more suitable for applications in academia than for mass-fabrication of lab-on-a-chip devices.

An embossing technique using lamination has been investigated by Paul et al. (2007) to replicate long channels ($\sim$10 cm), thus addressing the shortcomings of other replication methods in patterning long structures. The mould is fabricated by laminating a dry resist film on a substrate, e.g. glass or a thick film of poly(ethylene terephthalate), UV exposing and developing it. A Topas sheet (grade 8007, Topas Advanced Polymers GmbH) and the mould are placed in a laminator, where both rolls are heated to 130°C and a laminating speed of 0.5 m/min is applied. Early results indicate that higher laminating temperatures and lower laminating speeds should be used to have channels with vertical instead of sloped sidewalls.

3.2 Direct structuring

Laser ablation and micro milling are two techniques that can be used for rapid prototyping, due to the hardness and chemical inertness of the COP material.

3.2.1 Laser ablation

In laser ablation, the interaction of a high intensity laser beam with the material causes the latter to evaporate at the laser focal point (Malek 2006). Laser ablation has been used on other polymeric materials, such as PMMA (Johnson et al. 2001); however, so far, its use for microstructuring of COP has not been subject of any intensive study yet. Sabbert et al. (1999) presented some results using an ArF excimer laser ($\lambda = 193$ nm) and determined that the ablation depth of COP is 3.4 times lower than for PMMA. Nevertheless, Sabbert et al. claim that this lower ablation depth can be used to better control the depth of the device structures. Bundgaard et al. (2006), using a CO_2 laser, consider this limitation a severe constraint, since using COP only low aspect ratio and poorly defined structures could be fabricated. Sabbert et al. further analysed their results and revealed that for features not deeper than 200 µm, no debris is redeposited on the surface. However, for deeper structures, clusters ($\sim$100 nm) of redeposited material are visible close to the ablated holes. Ultrasonic treatment in isopropanol proved inefficient to remove these clusters.

A disadvantage of the ablation technique is that it can lead to changes in the surface chemistry of the polymer in comparison to the bulk properties (Johnson et al. 2001). This can be difficult to control and in applications where surface chemistry plays a major role (e.g. in electrokinetic separations) the performance of the device can be affected in an unpredictable way.

3.2.2 Milling

Mechanical milling of polymeric structures is a commonly used method for rapid prototyping. Milling consists of patterning a substrate by moving it against a rotating tool (mill or drill). The dimensions of the tool used affect both the resolution and the wall roughness.

Until now, not many results have been presented concerning milling of COP, due to the roughness of the fabricated structures. Rough surfaces are, for instance, detrimental for optical applications, where they scatter light. Grumann et al. (2006) used computer numerical control (CNC) micromachining to fabricate a COP lab-on-a-disk. The milled V-grooves, fabricated for deflecting a light beam by 90°, had a surface roughness low enough that it did not significantly influence the overall results. The roughness of structures milled in two different grades of Topas (grade 5013 and 8007, Topas Advanced Polymers GmbH) has been investigated by Bundgaard et al. (2006). A tool with a diameter of 200 µm was used and the average roughness was measured depending on the feed speed. 50 nm was the lowest average roughness obtained. The

Table 4 Overview of the different COP fabrication methods, where (+++) means excellent; (++) means good; (+) means acceptable and (−) means less suited. Feature size refers to the adaptability of the described processes for fabricating structures ranging from nm to cm in the same process step

Process	Throughput	Fast prototyping	Feature size
Injection moulding	+++	−	++
Hot embossing	+	+	++
Nanoimprint	+	+	+++
Laser ablation	++	+++	+
Micromilling	−	+++	+

roughness was shown to mainly dependent on the feed speed, varied between 10 and 60 mm/min, and the grade of Topas milled, with the more viscous grade giving the lower roughness.

Steigert et al. (2007) used milling as a simple and rapid way to integrate macrostructures next to microstructures that were previously imprinted in a COP substrate.

In order to provide a short overview of the fabrication section, Table 4 summarises the different COP fabrication methods in terms of their throughput, fast prototyping capabilities and ability to fabricate different structure sizes.

3.3 Bonding

Regularly, the fabrication of lab-on-a-chip systems involves a bonding step by which microfluidic channels can be sealed. Gluing is one of the most common bonding techniques, where a layer of glue is used to join two different polymer parts (Becker and Gartner 2000). However, this involves a potential risk that the glue layer flows into the microfabricated structures, e.g. leading to clogging of channels. Do and Ahn (2008) successfully used a room temperature UV adhesive to bond three distinct COP parts of a lab-on-a-chip system.

Cyclic olefin polymer (COP), as a thermoplastic polymer, is frequently bonded using thermal bonding (Bedair and Oleschuk 2006; Bhattacharyya and Klapperich 2006; Bilenberg et al. 2005; Choi et al. 2009; Gustafsson et al. 2008; Hansen et al. 2005; Kameoka et al. 2001; Kim et al. 2006; Li et al. 2005; Mair et al. 2006; Mela et al. 2005; Nilsson et al. 2005; Wallow et al. 2007; Yang et al. 2005a). Polymer chains in between the mating parts diffuse between the surfaces promoting adhesion. Using COP pieces with slightly different glass transition temperatures is a better choice, since then only one of the layers softens, avoiding deformation and obstruction of the microstructured features (Bilenberg et al. 2005; Gustafsson et al. 2008). Yang et al. (2005a, b) thermally bonded Zeonor substrates by heating them to the T_g of the polymer and pressing them together (~0.5 kN) for 5 min. After this step, the applied force was removed and the substrates were annealed at $T_g + 10°C$ for 10 min. This proved to increase the bond strength, so that a flow rate of 10 µl/min could be supported in the fluidic channel (Yang et al. 2005a). A similar annealing step has also been performed by Illa et al. (2009) resulting in a good quality bonding. Nevertheless, thermal bonding typically yields relatively low bond strength due to the low surface energy of thermoplastics. Several tests have been performed on how to improve the bond strength. O_2 plasma activation has been shown to be more effective compared to N_2 and N_2–O_2 plasma activation to improve the bond strength of COP substrates (Kettner et al. 2006). UV/ozone surface treatments have increased bonding strengths of 0.003 mJ/cm^2 for native (untreated) substrates up to 0.8 mJ/cm^2 under specific bonding conditions (Tsao et al. 2007). Improved diffusion of polymer chains, due to surface treatments, is seen as an explanation for closer contact between the mating surfaces. In thermal bonding, non-optimised parameters, such as temperature and pressure, may cause channel deformation. This issue has been circumvented by Steigert et al. (2007) and other groups where a lamination machine was used to bond two different grades of Topas. Experiments showed that pressures of 0.4 MPa could be applied to the fabricated channels (Steigert et al. 2007). Bond strength evaluation showed that temperature is the most important parameter in lamination (Fredrickson et al. 2006). Too high temperatures would lead to channel deformation, including to bending of the device, whereas too low temperatures are insufficient for bonding (Fredrickson et al. 2006).

Solvent bonding is another bonding technique especially suited for achieving high bond strengths required for some COP microfluidic devices (Chen et al. 2008b; Faure et al. 2008; Liu et al. 2007; Ro et al. 2006; Tsao et al. 2008; Wallow et al. 2007). Polymer solubility enables a better entanglement of the polymer chains, since these become more mobile across the bonding interface. A timed immersion of Zeonor (grade 1060R, Zeon Chemicals) pieces in an ethanol/decalin solution enables a high bond strength after thermal bonding (Wallow et al. 2007). Sealed microfluidic channels withstood pressures up to 13–16 MPa, without deformation of the structures beyond the thickness of the swollen layer (Wallow et al. 2007). Mair et al. (2006) improved the bonding technique used in their earlier chips by exposing one of the bonding surfaces to solvent vapour, bringing the mating surfaces into contact and then exposing the stack to UV light (Mair et al. 2007). This was done at room temperature to only promote a higher polymer chain mobility at the mating surfaces and not in the bulk. It led to an improved burst pressure of 34.6 MPa (Mair et al. 2007) compared to previous results of 15.6 MPa (Mair et al. 2006), both regarded as the highest in channel back pressure at the time of publication. A solvent mixture of hexadecane and isopropanol has also been used to bond COP sheets in a lamination machine (Paul et al. 2007).

Localised bonding (Tsao and Devoe 2009) is done by inducing heat and softening the interface between mating surfaces using ultrasonic energy. Another way of achieving localised welding is by depositing metallic films on the mating surfaces and heating them up using microwave energy. COP pieces can be bonded using infrared laser welding, due to COP transparency at this wavelength range. However, an opaque surface has to be used for energy absorption and localised heat generation, such as absorbing particles or special dyes (Bundgaard et al. 2006; Pfleging and Baldus 2006). In general, pigments absorbing in the near infrared range can be used to bond transparent polymers, such as COP (Clearweld, Gentex Corporation, UK or Lumogen, BASF AG, Germany). Pfleging and Baldus (2006) reported that at 20°C below the T_g COP was welded without any structural damage, using very thin carbon layers as an absorbing layer. The maximum bond strength was achieved for a temperature slightly under T_g. Despite the existence of these techniques, their application to microfluidic chips is not common practice (Tsao and Devoe 2009).

4 Applications

This section gives examples of how COP microsystems are used for various applications. First, implementations of different chemical analysis techniques, such as electrophoresis, chromatography, solid phase extraction (SPE), isoelectric focusing (IEF) and mass spectrometry (MS) are described. Then, chips with integrated optical elements and applications within blood and DNA analysis are presented. Other examples of COP microchips include magnetic immunoassays (Do and Ahn 2008), streaming potential detection (Pu et al. 2008) and light actuated microvalves (Chen et al. 2008b).

4.1 Microchip electrophoresis

In capillary electrophoresis, a high voltage is applied between the ends of a narrow capillary, separating analytes depending on the ratio between their charge and viscous drag. Transferring the technique from capillaries to microchannels has resulted in faster separations. Moreover, integration of other functionalities, such as sample preconcentration (Sueyoshi et al. 2008), electrokinetic sample injection (Bias et al. 2008) and waveguides for fluorescence (Bliss et al. 2007) or absorbance (Mogensen et al. 2001) detection, is also possible. It is therefore not surprising that this is a common application for microfluidic COP chips as well. Several different detection methods have been employed in COP electrophoresis chips, e.g. electrochemical detection (Castano-Alvarez et al. 2005, 2006a, b, 2007), fluorescence detection (Hurth et al. 2008; Yi et al. 2008) and MS (Kameoka et al. 2001; Shinohara et al. 2008).

Commercial Topas electrophoresis chips consisting of an injection cross and a straight separation channel are already available, e.g. from Microfluidic ChipShop (Jena, Germany; Microfluidic Chipshop 2009). Chips from this company have been evaluated by Castano-Alvarez et al. (2005, 2006a, b, 2007) and compared to PMMA. The electroosmotic mobility was higher for Topas than for PMMA, but approximately halved compared to glass. The slightly more expensive Topas chips turned out to be more durable than the PMMA chips (~100 runs for Topas compared to ~50 runs for PMMA). Yi et al. (2008) compared electrophoretic separations in Zeonex and PMMA chips. In their findings, the Zeonex chips had lower background fluorescence, higher electrophoretic efficiency and better reproducibility for separation of Cy3 and Cy5 dyes. For DNA samples, the Zeonex chips displayed higher signal to noise ratio, whilst the PMMA chips provided a higher degree of separation.

4.2 Chromatography and solid phase extraction

In chromatography, analytes are separated depending on how much they are slowed down due to their affinity to a stationary phase. Solid phase extraction (SPE) is a related method where either the analytes of interest or the undesired impurities are completely retained by the stationary phase. These methods are usually performed in columns and syringes, but have also been transferred to microfluidics. The main challenge is then to create a stationary phase in the microfluidic channel. The optical and chemical properties of COP polymers have turned out useful for this purpose.

One method is to use the partial UV transparency of COPs for photo-initiated polymerisation (Stachowiak et al. 2003). The channel surface is first modified by photo-initiated graft polymerisation to make it possible to attach a stationary phase. Then, a stationary phase is created by photo-initiated polymerisation of a porous polymer in the channels (Fig. 5). This method has been used by several groups for various purposes. SPE of DNA in porous polymer containing silica microspheres was demonstrated by Bhattacharyya and Klapperich (2006). Yang et al. (2005b) also used the porous polymer for preconcentration by SPE. In this case, analytes were retained by the stationary phase and subsequently eluted and analysed by electrospray ionisation mass spectrometry (ESI-MS). Ro et al. describe a system to perform chromatography of peptides and proteins, which were then directly deposited by a pulsed electrical field onto a matrix assisted laser desorption/ionisation time-of-flight mass spectrometry

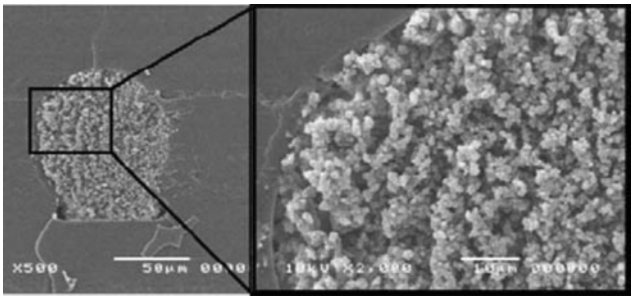

Fig. 5 SEM image of chromatography channels with photo-polymerised porous polymer (Ro et al. 2006)

(MALDI-TOF-MS) target (Liu et al. 2007; Ro et al. 2006). Reversed phase electrochromatography with fluorescence detection was demonstrated by Faure et al. (2008) with the porous polymer as stationary phase.

Another method to create a stationary phase is to increase the surface area using microfabricated structures. Gustafsson et al. (2008) used the hydrophobic COP polymer directly as stationary phase. A microfluidic chip with an injection cross and a chromatography channel was fabricated by NIL in a 7 μm thick layer of Topas spun over a glass substrate. The chromatography channel contained approximately 120,000 hexagonal pillars, as shown in Fig. 4. The higher regularity of microfabricated structures compared to traditionally packed bed columns is expected to improve the efficiency of the separation. In order to demonstrate the function of the chip, three fluorescently labelled amines were separated by reversed phase electrochromatography. Illa et al. (2009) also used a COP polymer directly as stationary phase, but this time for pressure-driven chromatography. They successfully separated coumarin dyes in a hot-embossed chip.

4.3 Isoelectric focusing

In isoelectric focusing (IEF), an electrical potential is applied through a channel containing the analytes and a pH gradient, separating the analytes depending on their isoelectric point (pI). When this is performed in COP microchips, the hydrophobicity of the surface can cause protein adsorption, whilst the electroosmotic flow may disrupt the separation. These problems can, however, be solved by applying a dynamic coating of hydroxyethyl cellulose (HEC; Zhang et al. 2008), or using the partial UV transparency of COPs to photograft a polyacrylamide coating (Li et al. 2005).

Das et al. (2007a, b) integrated IEF with multi-channel polyacrylamide gel electrophoresis (PAGE) for protein separation. IEF is first performed in one channel and PAGE is then carried out in multiple channels perpendicular to the IEF channel, as illustrated in Fig. 6. The partial UV transparency of the COP material was here utilised to photo-initiate in situ gel polymerisation, to form pseudo-valves at the inlet to the PAGE channels. They prevent mixing of the two separation media, whilst proteins can be pumped through these barriers electrokinetically.

4.4 Mass spectrometry

In mass spectrometry (MS), the analytes are ionised, accelerated and separated depending on their path in an electric and/or magnetic field. COP chips have been used as electrospray emitters, where the liquid sample is ionised and turned into an aerosol (Kameoka et al. 2002; Liu et al. 2007; Park et al. 2008a; Shinohara et al. 2008; Yang et al. 2004, 2005a, b). Bedair and Oleschuk (2006) reduced clogging and droplet spreading problems by utilising a porous polymer monolith at the end of the channel. They compared emitters fabricated in PDMS, COP and PMMA, where COP emitters showed the highest chip-to-chip reproducibility for the MS data. This is most likely because the COP is more compatible with the UV light and solvents used for the formation of the porous polymer monoliths.

An alternative to electrospray ionisation is matrix assisted laser desorption/ionisation (MALDI), where the

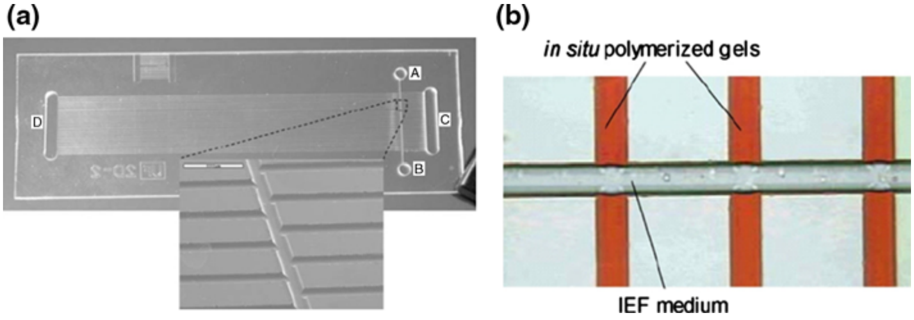

Fig. 6 **a** Optical image of a COP device for 2D protein separation. The proteins are first separated by IEF in the channel from *A* to *B* and then by polyacrylamide gel electrophoresis (PAGE) in the parallel channels from *C* to *D*. The *inset* shows an SEM image of channel intersections (Das et al. 2007b). **b** Micrograph of the channel intersections with in situ polymerised gel pseudo-valves (Das et al. 2007a)

sample is deposited onto a target, and subsequently, vaporised and ionised by a laser beam. Ro et al. (2006) performed liquid chromatography in COP chips followed by deposition onto a MALDI target. COP chips have also been used to add other functions prior to MS, such as microchip electrophoresis (MCE; Kameoka et al. 2001; Shinohara et al. 2008), SPE (Yang et al. 2005b) or enzymatic reactions (Benetton et al. 2003).

4.5 Integrated optics

Cyclic olefin polymers (COPs) are attractive for micro-optics, since it is highly transparent at shorter wavelengths, more so than many other polymers (Topas Advanced Polymers 2009). Microlenses (Appasamy et al. 2005) and photonic crystals (Bilenberg et al. 2006) have for instance been fabricated. Still there are surprisingly few examples of microfluidics with integrated optics in COP.

One example is the study of Nilsson et al. (2005) who fabricated a microfluidic dye laser coupled to waveguides. The laser was later integrated with Fresnel lenses to couple light in and out of the waveguides, a microfluidic mixer and an absorbance cell (Fig. 7a; Hansen et al. 2005). Another example of waveguides with a COP core was recently published by Okagbare et al. (2010). The waveguides were fabricated by curing COP solution in channels in a PMMA substrate. It was subsequently bonded to another PMMA substrate containing microfluidic channels in the orthogonal direction. The assembly was used for evanescent fluorescence excitation of fluorophores in the channels. However, to the best of our knowledge, no waveguides have yet been published where both the core and cladding are made from COP materials. This should, in theory, be possible, since there is a small difference in refractive index between different COP materials and grades.

With their combination of excellent optical and chemical properties, COP polymers are likely to become increasingly popular within optofluidics. For this to happen, more research is needed, e.g. within fabrication and characterisation of COP waveguides.

4.6 Blood analysis

Many clinically relevant parameters can be measured in blood samples, making blood analysis an important area for microfluidics. Ahn et al. (2004) developed a COP chip for electrochemical measurement of oxygen, glucose and lactate in blood. Liquids on the chip are controlled by passive valves and pressurised air stored on-chip. The pressurised air is released by melting of thermoplastic membranes by localised heaters. In this way, bulky and power consuming pumps can be omitted. They list several reasons for choosing COP as substrate material instead of PC and PMMA. These include lower water absorption, excellent adhesion for most metallic films, resistance to most polar solvents and better properties for injection moulding.

Grumann et al. (2006) also developed an assay capable of measuring glucose levels in blood. In this COP "lab-on-a-disk", sample and reagent are driven by centrifugal forces through passive hydrophobic valves into a detection cell, where the glucose level is read via an optical transmission measurement. The optical path length is increased by V-groves reflecting the light into and out of the plane of the disk.

Jang et al. (2006) fabricated a chip from COP, dry film resist, PDMS and gold where blood plasma is separated from cells by micropillars. The blood is pumped through the pillar array by an integrated micropump, consisting of a heater and a flexible membrane.

Cyclic olefin polymer (COP) chips for blood typing by agglutination have also been demonstrated. In these chips,

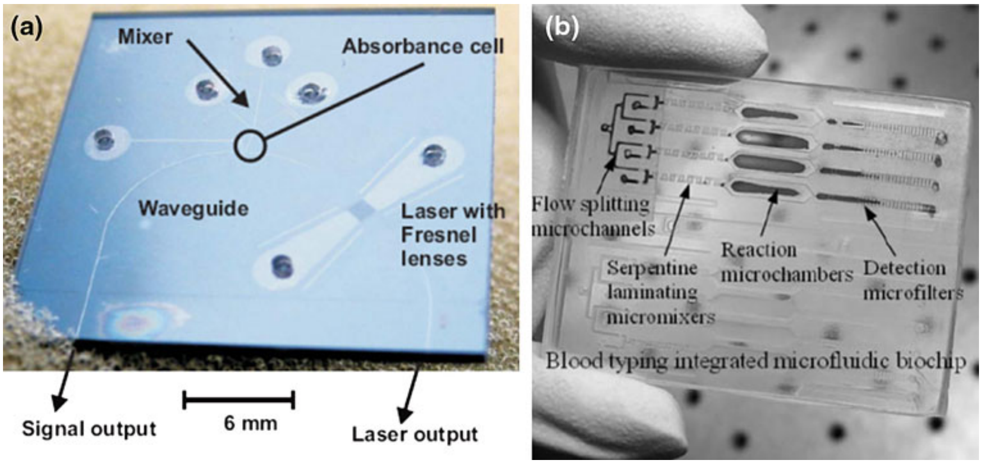

Fig. 7 **a** Image of a microfluidic chip where the dye laser is integrated with waveguides, Fresnel lenses, a mixer, and an absorbance cell (Hansen et al. 2005). **b** Picture of a blood typing chip prototype (Kim et al. 2006)

blood and reagents are mixed in serpentine laminating micromixers. The result can be read by eye either as the degree of light transmission through a microwell (Choi et al. 2009) or by how far sample reaches in an array of microfilters with decreasing gap sizes (Fig. 7b; Kim et al. 2006).

4.7 DNA analysis

Analysis of DNA or RNA is useful for identifying a virus or bacteria, and for analysing a patients genetical predisposition for developing a certain disease or responding to a treatment. Several COP chips have been developed for this purpose. As mentioned before, Bhattacharyya and Klapperich (2006) concentrated DNA by SPE. The DNA was retained by a porous monolithic polymer column impregnated with silica particles, and subsequently eluted.

Larsen et al. (2008) detected single nucleotide polymorphisms (SNPs), important for both forensics and the detection of genetic disease factors. They attached the mutant and wild-type sequence to beads of different size, which were then separated by pinched flow fractionation. Gulliksen et al. (2005) amplified mRNA by real-time nucleic acid sequence-based amplification (NASBA), to detect markers for cervical cancer. There are also examples of MCE of DNA with both fluorescence (Hurth et al. 2008) and electrochemical detection (Castano-Alvarez et al. 2007) using COP microchips.

5 Conclusions and outlook

Recently, COP polymers have emerged as an interesting alternative to the most common polymers used in microfluidics. COP polymers have several favourable properties, such as low water absorption, high transmission in the near UV range and good chemical resistance.

There is a wide array of fabrication methods available. In order to choose the most suitable one, it is important to consider the resolution, surface roughness and manufacturing cost. Replication methods, such as injection moulding, hot embossing and NIL, are the ones most commonly used. Direct structuring of COP by laser ablation and micromilling has also been demonstrated. These methods are more convenient for fast prototyping, but have not yet been widely used and need further investigation.

COP polymers are increasingly popular for microfluidics and a multitude of chemical analysis techniques have already been implemented, e.g. electrophoresis, chromatography, SPE, IEF and MS. Surprisingly, few examples of microfluidic COP chips with integrated optics have been reported. COPs are, however, likely to have a bright future in optofluidics, considering their exceptional optical and chemical properties compared to other polymers.

In conclusion, we expect COP polymers to further increase in popularity for microfluidics, in particular optofluidics, due to their unique properties and ease of fabrication.

Acknowledgements This study was partially supported by the Danish Research Council (FTP grant #274-06-0193) and by the NeuroTAS project, financially supported by the European Commission through the Sixth Framework Programme.

References

Abgrall P, Conedera V, Camon H, Gue AM, Nguyen NT (2007) SU-8 as a structural material for labs-on-chips and microelectromechanical systems. Electrophoresis 28(24):4539–4551

Ace Glass I (2010) Available at http://www.aceglass.com/dpro/attachment_kb.php?id=6. Accessed February 2010

Ahn CH, Choi JW, Beaucage G, Nevin JH, Lee JB, Puntambekar A, Lee JY (2004) Disposable Smart lab on a chip for point-of-care clinical diagnostics. Proc IEEE 92(1):154–173

Angelov AK, Coulter JP (2008) The development and characterization of polymer microinjection molded gratings. Polym Eng Sci 48(11):2169–2177

Appasamy S, Li WZ, Lee SH, Boyd JT, Ahn CH (2005) High-throughput plastic microlenses fabricated using microinjection molding techniques. Opt Eng 44(12):123401-1–123401-8

Attia UM, Marson S, Alcock JR (2009) Micro-injection moulding of polymer microfluidic devices. Microfluid Nanofluid 7(1):1–28

Becker H, Gartner C (2000) Polymer microfabrication methods for microfluidic analytical applications. Electrophoresis 21(1):12–26

Becker H, Gartner C (2008) Polymer microfabrication technologies for microfluidic systems. Anal Bioanal Chem 390(1):89–111

Becker H, Locascio LE (2002) Polymer microfluidic devices. Talanta 56(2):267–287

Bedair MF, Oleschuk RD (2006) Fabrication of porous polymer monoliths in polymeric microfluidic chips as an electrospray emitter for direct coupling to mass spectrometry. Anal Chem 78(4): 1130–1138

Benetton S, Kameoka J, Tan AM, Wachs T, Craighead H, Henion JD (2003) Chip-based P450 drug metabolism coupled to electrospray ionization-mass spectrometry detection. Anal Chem 75(23): 6430–6436

Bhattacharyya A, Klapperich CM (2006) Thermoplastic microfluidic device for on-chip purification of nucleic acids for disposable diagnostics. Anal Chem 78(3):788–792

Bias M, Delaunay N, Rocca JL (2008) Electrokinetic-based injection modes for separative microsystems. Electrophoresis 29(1):20–32

Bilenberg B, Nielsen T, Clausen B, Kristensen A (2004) PMMA to SU-8 bonding for polymer based lab-on-a-chip systems with integrated optics. J Micromech Microeng 14(6):814–818

Bilenberg B, Hansen M, Johansen D, Ozkapici V, Jeppesen C, Szabo P, Obieta IM, Arroyo O, Tegenfeldt JO, Kristensen A (2005) Topas-based lab-on-a-chip microsystems fabricated by thermal nanoimprint lithography. J Vac Sci Technol B 23(6):2944–2949

Bilenberg B, Frandsen LH, Nielsen T, Vogler M, Borel PI, Kristensen A (2006) Nanoimprint lithography of topology optimized photonic crystal devices. Conference on lasers and electro-optics and 2006 Quantum Electronics and Laser Science Conference in Long Beach, USA, IEEE

Bliss CL, McMullin JN, Backhouse CJ (2007) Rapid fabrication of a microfluidic device with integrated optical waveguides for DNA fragment analysis. Lab Chip 7:1280–1287

Bundgaard F, Perozziello G, Geschke O (2006) Rapid prototyping tools and methods for all-Topas (R) cyclic olefin copolymer fluidic microsystems. Proc IME C J Mech Eng Sci 220(11):1625–1632

Castano-Alvarez M, Fernandez-Abedul MT, Costa-Garcia A (2005) Poly(methylmethacrylate) and Topas capillary electrophoresis microchip performance with electrochemical detection. Electrophoresis 26(16):3160–3168

Castano-Alvarez M, Fernandez-Abedul MT, Costa-Garcia A (2006a) Amperometric detector designs for capillary electrophoresis microchips. J Chrom 1109(2):291–299

Castano-Alvarez M, Fernandez-Abedul MT, Costa-Garcia A (2006b) Analytical performance of CE microchips with amperometric detection. Instrum Sci Tech 34(6):697–710

Castano-Alvarez M, Fernandez-Abedul M, Costa-Garcia A (2007) Electroactive intercalators for DNA analysis on microchip electrophoresis. Electrophoresis 28(24):4679–4689

Chen CM, Chang GL, Lin CH (2008a) Performance evaluation of a capillary electrophoresis electrochemical chip integrated with gold nanoelectrode ensemble working and decoupler electrodes. J Chrom 1194(2):231–236

Chen GF, Svec F, Knapp DR (2008b) Light-actuated high pressure-resisting microvalve for on-chip flow control based on thermo-responsive nanostructured polymer. Lab Chip 8(7):1198–1204

Choi SH, Kim DS, Kwon TH (2009) Microinjection molded disposable microfluidic lab-on-a-chip for efficient detection of agglutination. Microsyst Technol 15(2):309–316

Christensen TB, Bang DD, Wolff A (2008) Multiplex polymerase chain reaction (PCR) on a SU-8 chip. Microelectron Eng 85(5–6):1278–1281

Das C, Fredrickson CK, Xia Z, Fan ZH (2007a) Device fabrication and integration with photodefinable microvalves for protein separation. Sensor Actuator Phys 134(1):271–277

Das C, Zhang J, Denslow ND, Fan ZH (2007b) Integration of isoelectric focusing with multi-channel gel electrophoresis by using microfluidic pseudo-valves. Lab Chip 7(12):1806–1812

Dhouib K, Malek CK, Pfleging W, Gauthier-Manuel B, Duffait R, Thuillier G, Ferrigno R, Jacquamet L, Ohana J, Ferrer JL, Theobald-Dietrich A, Giege R, Lorber B, Sauter C (2009) Microfluidic chips for the crystallization of biomacromolecules by counter-diffusion and on-chip crystal X-ray analysis. Lab Chip 9(10):1412–1421

Do J, Ahn CH (2008) A polymer lab-on-a-chip for magnetic immunoassay with on-chip sampling and detection capabilities. Lab Chip 8(4):542–549

Faure K, Albert M, Dugas V, Cretier G, Ferrigno R, Morin P, Rocca JL (2008) Development of an acrylate monolith in a cyclo-olefin copolymer microfluidic device for chip electrochromatography separation. Electrophoresis 29(24):4948–4955

Fredrickson CK, Xia Z, Das C, Ferguson R, Tavares FT, Fan ZH (2006) Effects of fabrication process parameters on the properties of cyclic olefin copolymer microfluidic devices. IEEE ASME J Microelectromech Syst 15(5):1060–1068

Gadegaard N, Mosler S, Larsen NB (2003) Biomimetic polymer nanostructures by injection molding. Macromol Mater Eng 288(1):76–83

Gerlach A, Knebel G, Guber AE, Heckele M, Herrmann D, Muslija A, Schaller T (2002) High-density plastic microfluidic platforms for capillary electrophoresis separation and high-throughput screening. Sensor Mater 14(3):119–128

Gourgon C, Perret C, Tallal J, Lazzarino F, Landis S, Joubert O, Pelzer R (2005) Uniformity across 200 mm silicon wafers printed by nanoimprint lithography. J Phys D-Appl Phys 38(1):70–73

Grumann M, Steigert J, Riegger L, Moser I, Enderle B, Riebeseel K, Urban G, Zengerle R, Ducree J (2006) Sensitivity enhancement for colorimetric glucose assays on whole blood by on-chip beam-guidance. Biomed Microdevices 8(3):209–214

Gulliksen A, Solli LA, Drese KS, Sorensen O, Karlsen F, Rogne H, Hovig E, Sirevag R (2005) Parallel nanoliter detection of cancer markers using polymer microchips. Lab Chip 5(4):416–420

Guo YL, Uchiyama K, Nakagama T, Shimosaka T, Hobo T (2005) An integrated microfluidic device in polyester for electrophoretic analysis of amino acids. Electrophoresis 26(9):1843–1848

Gustafsson O, Mogensen KB, Kutter JP (2008) Underivatized cyclic olefin copolymer as substrate material and stationary phase for capillary and microchip electrochromatography. Electrophoresis 29(15):3145–3152

Hansen M, Nilsson D, Johansen DM, Balslev S, Kristensen A (2005) A nanoimprinted polymer lab-on-a-chip with integrated optics. Conference on advancements in polymer optics design, fabrication and materials in San Diego, USA, SPIE Symposium on Optics and Photonics

Hawkins KR, Yager P (2003) Nonlinear decrease of background fluorescence in polymer thin-films: a survey of materials and how they can complicate fluorescence detection in μTAS. Lab Chip 3(4):248–252

Huang WJ, Chang FC, Chu PPJ (2000) Functionalization and chemical modification of cyclo olefin copolymers (COC). Polymer 41(16):6095–6101

Hurth C, Lenigk R, Zenhausern F (2008) A compact LED-based module for DNA capillary electrophoresis. Appl Phys B 93(2–3):693–699

Hwang SJ, Yu HH (2005) Novel cyclo olefin copolymer used as waveguide film. Jpn J Appl Phys 44(4B):2541–2545

Hwang SJ, Tseng MC, Shu JR, Yu HH (2008) Surface modification of cyclic olefin copolymer substrate by oxygen plasma treatment. Surf Coating Tech 202(15):3669–3674

Illa X, De Malsche W, Bomer J, Gardeniers H, Eijkel J, Morante JR, Romano-Rodriguez A, Desmet G (2009) An array of ordered pillars with retentive properties for pressure-driven liquid chromatography fabricated directly from an unmodified cyclo olefin polymer. Lab Chip 9(11):1511–1516

Ito H, Kazama K, Kikutani T (2007) Effects of process conditions on surface replication and higher-order structure formation in micromolding. Macromol Symp 249–250(1):628–634

Jang WI, Chung KH, Pyo HB, Park SH (2006) Self-operated blood plasma separation using micropump in polymer-based microfluidic device. Proc SPIE 6415:641512

Japan Synthetic Rubber (2009) Available at http://www.jsr.co.jp/jsr_e/pd/arton/at01.html. Accessed April 2009

Johansson BL, Larsson A, Ocklind A, Ohrlund A (2002) Characterization of air plasma-treated polymer surfaces by ESCA and contact angle measurements for optimization of surface stability and cell growth. J Appl Polymer Sci 86(10):2618–2625

Johnson TJ, Waddell EA, Kramer GW, Locascio LE (2001) Chemical mapping of hot-embossed and UV-laser- ablated microchannels in poly(methyl methacrylate) using carboxylate specific fluorescent probes. Appl Surf Sci 181(1–2):149–159

Kalima V, Pietarinen J, Siitonen S, Immonen J, Suvanto M, Kuittinen M, Monkkonen K, Pakkanen TT (2007) Transparent thermoplastics: replication of diffractive optical elements using micro-injection molding. Opt Mater 30(2):285–291

Kameoka J, Craighead HG, Zhang HW, Henion J (2001) A polymeric microfluidic chip for CE/MS determination of small molecules. Anal Chem 73(9):1935–1941

Kameoka J, Orth R, Ilic B, Czaplewski D, Wachs T, Craighead HG (2002) An electrospray ionization source for integration with microfluidics. Anal Chem 74(22):5897–5901

Kee JS, Poenar DP, Neuzil P, Yobas L (2008) Monolithic integration of poly(dimethylsiloxane) waveguides and microfluidics for on-chip absorbance measurements. Sens Actuat B 134(2):532–538

Kettner P, Pelzer RL, Glinsner T, Farrens S, Lee D (2006) New results on plasma activated bonding of imprinted polymer features for bio MEMS applications. J Phys 34:65–71

Khanarian G, Celanese H (2001) Optical properties of cyclic olefin copolymers. Opt Eng 40(6):1024–1029

Kim DS, Lee SH, Ahn CH, Lee JY, Kwon TH (2006) Disposable integrated microfluidic biochip for blood typing by plastic microinjection moulding. Lab Chip 6(6):794–802

Lamonte RR, McNally D (2001) Cyclic olefin copolymers. Adv Mater Process 159:33–36

Larsen AV, Poulsen L, Birgens H, Dufva M, Kristensen A (2008) Pinched flow fractionation devices for detection of single nucleotide polymorphisms. Lab Chip 8(5):818–821

Lee DS, Yang H, Chung KH, Pyo HB (2005) Wafer-scale fabrication of polymer-based microdevices via injection molding and photolithographic micropatterning protocols. Anal Chem 77(16): 5414–5420

Li C, Yang YN, Craighead HG, Lee KH (2005) Isoelectric focusing in cyclic olefin copolymer microfluidic channels coated by polyacrylamide using a UV photografting method. Electrophoresis 26(9):1800–1806

Liu J, Ro KW, Nayak R, Knapp DR (2007) Monolithic column plastic microfluidic device for peptide analysis using electrospray from a channel opening on the edge of the device. Int J Mass Spectrom 259(1–3):65–72

Mair DA, Geiger E, Pisano AP, Frechet JMJ, Svec F (2006) Injection molded microfluidic chips featuring integrated interconnects. Lab Chip 6(10):1346–1354

Mair DA, Rolandi M, Snauko M, Noroski R, Svec F, Frechet JMJ (2007) Room-temperature bonding for plastic high-pressure microfluidic chips. Anal Chem 79(13):5097–5102

Malek CGK (2006) Laser processing for bio-microfluidics applications (part I). Anal Bioanal Chem 385(8):1351–1361

McCormick RM, Nelson RJ, Alonso-Amigo MG, Benvegnu J, Hooper HH (1997) Microchannel electrophoretic separations of DNA in injection-molded plastic substrates. Anal Chem 69(14): 2626–2630

McDonald JC, Duffy DC, Anderson JR, Chiu DT, Wu HK, Schueller OJA, Whitesides GM (2000) Fabrication of microfluidic systems in poly(dimethylsiloxane). Electrophoresis 21(1):27–40

Mela P, van den Berg A, Fintschenko Y, Cummings EB, Simmons BA, Kirby BJ (2005) The zeta potential of cyclo-olefin polymer microchannels and its effects on insulative (electrodeless) dielectrophoresis particle trapping devices. Electrophoresis 26(9): 1792–1799

Microchem (2009) Available at http://www.microchem.com/products/su_eight.htm. Accessed April 2009

Microfluidic ChipShop (2009) Available at http://www.microfluidic-chipshop.com. Accessed June 2009

Mitsui Chemicals America (2009) Available at http://www.mitsuichemicals.com/apel.htm. Accessed April 2009

Mogensen KB, Petersen NJ, Hubner J, Kutter JP (2001) Monolithic integration of optical waveguides for absorbance detection in microfabricated electrophoresis devices. Electrophoresis 22(18): 3930–3938

Mogensen KB, El-Ali J, Wolff A, Kutter JP (2003) Integration of polymer waveguides for optical detection in microfabricated chemical analysis systems. Appl Optic 42(19):4072–4079

Monkkonen K, Lautanen J, Kettunen V, Leppanen VP, Pakkanen TT, Jaaskelainen T (2000) Replication of an antireflecting element in COC plastics using a hot embossing technique. J Mater Chem 10(12):2634–2636

Monkkonen K, Hietala J, Paakkonen P, Paakkonen EJ, Kaikuranta T, Pakkanen TT, Jaaskelainen T (2002) Replication of sub-micron features using amorphous thermoplastics. Polym Eng Sci 42(7): 1600–1608

Mosaddegh P, Angstadt DC (2008) Micron and sub-micron feature replication of amorphous polymers at elevated mold temperature without externally applied pressure. J Micromech Microeng 18(3): 035036

Nielsen T, Nilsson D, Bundgaard F, Shi P, Szabo P, Geschke O, Kristensen A (2004) Nanoimprint lithography in the cyclic olefin copolymer, Topas((R)), a highly ultraviolet-transparent and chemically resistant thermoplast. J Vac Sci Technol B 22(4): 1770–1775

Nikolova D, Dayss E, Leps G, Wutzler A (2004) Surface modification of cycloolefinic copolymers for optimization of the adhesion to metals. Surf Interface Anal 36(8):689–693

Nilsson D, Balslev S, Kristensen A (2005) A microfluidic dye laser fabricated by nanoimprint lithography in a highly transparent and chemically resistant cyclo-olefin copolymer (COC). J Micromech Microeng 15(2):296–300

Okagbare PI, Emory JM, Datta P, Goettert J, Soper SA (2010) Fabrication of a cyclic olefin copolymer planar waveguide embedded in a multi-channel poly(methyl methacrylate) fluidic chip for evanescence excitation. Lab Chip 10:66–73

Park SM, Lee KH, Craighead HG (2008a) On-chip coupling of electrochemical pumps and an SU-8 tip for electrospray ionization mass spectrometry. Biomed Microdevices 10(6):891–897

Park SW, Lee JH, Yoon HC, Kim BW, Sim SJ, Chae H, Yang SS (2008b) Fabrication and testing of a PDMS multi-stacked hand-operated LOC for use in portable immunosensing systems. Biomed Microdevices 10(6):859–868

Paul D, Pallandre A, Miserere S, Weber J, Viovy JL (2007) Lamination-based rapid prototyping of microfluidic devices using flexible thermoplastic substrates. Electrophoresis 28(7):1115–1122

Pfleging W, Baldus O (2006) Laser patterning and welding of transparent polymers for microfluidic device fabrication. Proc SPIE 6107:610705

Piruska A, Nikcevic I, Lee SH, Ahn C, Heineman WR, Limbach PA, Seliskar CJ (2005) The autofluorescence of plastic materials and chips measured under laser irradiation. Lab Chip 5(12):1348–1354

Pu QS, Elazazy MS, Alvarez JC (2008) Label-free detection of heparin, streptavidin, and other probes by pulsed streaming potentials in plastic microfluidic channels. Anal Chem 80(17):6532–6536

Ro KW, Liu H, Knapp DR (2006) Plastic microchip liquid chromatography-matrix-assisted laser desorption/ionization mass spectrometry using monolithic columns. J Chrom 1111(1):40–47

Rotting O, Ropke W, Becker H, Gartner C (2002) Polymer microfabrication technologies. Microsyst Technol 8(1):32–36

Sabbert D, Landsiedel J, Bauer HD, Ehrfeld W (1999) ArF-excimer laser ablation experiments on cycloolefin copolymer (COC). Appl Surf Sci 150(1–4):185–189

Shin JY, Park JY, Liu CY, He JS, Kim SC (2005) Chemical structure and physical properties of cyclic olefin copolymers—(IUPAC technical report). Pure Appl Chem 77(5):801–814

Shinohara H, Suzuki T, Kitagawa F, Mizuno J, Otsuka K, Shoji S (2008) Polymer microchip integrated with nano-electrospray tip for electrophoresis-mass spectrometry. Sens Actuat B 132(2):368–373

Sia SK, Whitesides GM (2003) Microfluidic devices fabricated in poly(dimethylsiloxane) for biological studies. Electrophoresis 24(21):3563–3576

Sikanen T, Tuomikoski S, Ketola RA, Kostiainen R, Franssila S, Kotiaho T (2007) Fully microfabricated and integrated SU-8-based capillary electrophoresis-electrospray ionization microchips for mass spectrometry. Anal Chem 79(23):9135–9144

Stachowiak TB, Rohr T, Hilder EF, Peterson DS, Yi MQ, Svec F, Frechet JMJ (2003) Fabrication of porous polymer monoliths covalently attached to the walls of channels in plastic microdevices. Electrophoresis 24(21):3689–3693

Stachowiak TB, Mair DA, Holden TG, Lee LJ, Svec F, Frechet JMJ (2007) Hydrophilic surface modification of cyclic olefin copolymer microfluidic chips using sequential photografting. J Separ Sci 30(7):1088–1093

Steffen H, Schröder K, Busse B, Ohl A, Weltmann K (2007) Functionalization of COC surfaces by Microwave Plasmas. Plasma Process Polymer 4:S392–S396

Steigert J, Haeberle S, Brenner T, Muller C, Steinert CP, Koltay P, Gottschlich N, Reinecke H, Ruhe J, Zengerle R, Ducree J (2007) Rapid prototyping of microfluidic chips in COC. J Micromech Microeng 17(2):333–341

Sueyoshi K, Kitagawa F, Otsuka K (2008) Recent progress of online sample preconcentration techniques in microchip electrophoresis. J Separ Sci 31(14):2650–2666

Tan HY, Loke WK, Tan YT, Nguyen NT (2008) A lab-on-a-chip for detection of nerve agent sarin in blood. Lab Chip 8(6):885–891

Toft KN, Vestergaard B, Nielsen SS, Snakenborg D, Jeppesen MG, Jacobsen JK, Arleth L, Kutter JP (2008) High-throughput Small Angle X-ray Scattering from proteins in solution using a microfluidic front-end. Anal Chem 80(10):3648–3654

Topas Advanced Polymers (2009) Available at http://www.topas.com/products-topas_coc. Accessed April 2009

Tsao CW, DeVoe DL (2009) Bonding of thermoplastic polymer microfluidics. Microfluid Nanofluid 6(1):1–16

Tsao CW, Hromada L, Liu J, Kumar P, DeVoe DL (2007) Low temperature bonding of PMMA and COC microfluidic substrates using UV/ozone surface treatment. Lab Chip 7(4):499–505

Tsao CW, Liu J, Devoe DL (2008) Droplet formation from hydrodynamically coupled capillaries for parallel microfluidic contact spotting. J Micromech Microeng 18(2):7

Wallow TI, Morales AM, Simmons BA, Hunter MC, Krafcik KL, Domeier LA, Sickafoose SM, Patel KD, Gardea A (2007) Low-distortion, high-strength bonding of thermoplastic microfluidic devices employing case-II diffusion-mediated permeant activation. Lab Chip 7(12):1825–1831

Wang YX, Zhou Y, Balgley BM, Cooper JW, Lee CS, DeVoe DL (2005) Electrospray interfacing of polymer microfluidics to MALDI-MS. Electrophoresis 26(19):3631–3640

Wang YR, Chen HW, He QH, Soper SA (2008) A high-performance polycarbonate electrophoresis microchip with integrated three-electrode system for end-channel amperometric detection. Electrophoresis 29(9):1881–1888

Yang YN, Kameoka J, Wachs T, Henion JD, Craighead HG (2004) Quantitative mass spectrometric determination of methylphenidate concentration in urine using an electrospray ionization source integrated with a polymer microchip. Anal Chem 76(9):2568–2574

Yang YN, Li C, Kameoka J, Lee KH, Craighead HG (2005a) A polymeric microchip with integrated tips and in situ polymerized monolith for electrospray mass spectrometry. Lab Chip 5(8):869–876

Yang YN, Li C, Lee KH, Craighead HG (2005b) Coupling on-chip solid-phase extraction to electrospray mass spectrometry through an integrated electrospray tip. Electrophoresis 26(19):3622–3630

Yi L, Wang XD, Fan Y (2008) Microfluidic chip made of COP (cyclo-olefin polymer) and comparion to PMMA (polymethylmethacrylate) microfluidic chip. J Mater Process Tech 208(1–3):63–69

Yoo YE, Kim TH, Choi DS, Lee HJ, Choi J, Kim SK (2009) Study on molding of a nanostructured plastic plate and its surface properties. Jpn J Appl Phys 48(6):06HF07

Zeon Chemicals (2009) Available at http://www.zeonex.com/default.asp. Accessed April 2009

Zhang J, Das C, Fan ZH (2008) Dynamic coating for protein separation in cyclic olefin copolymer microfluidic devices. Microfluid Nanofluid 5(3):327–335