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Biomedical microfluidic devices by using low-cost fabrication techniques: A review

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ABSTRACT

One of the most popular methods to fabricate biomedical microfluidic devices is by using a soft-lithography technique. However, the fabrication of the moulds to produce microfluidic devices, such as SU-8 moulds, usually requires a cleanroom environment that can be quite costly. Therefore, many efforts have been made to develop low-cost alternatives for the fabrication of microstructures, avoiding the use of cleanroom facilities. Recently, low-cost techniques without cleanroom facilities that feature aspect ratios more than 20, for fabricating those SU-8 moulds have been gaining popularity among biomedical research community. In those techniques, Ultraviolet (UV) exposure equipment, commonly used in the Printed Circuit Board (PCB) industry, replaces the more expensive and less available Mask Aligner that has been used in the last 15 years for SU-8 patterning. Alternatively, non-lithographic low-cost techniques, due to their ability for large-scale production, have increased the interest of the industrial and research community to develop simple, rapid and low-cost microfluidic structures. These alternative techniques include Print and Peel methods (PAP), laserjet, solid ink, cutting plotters or micromilling, that use equipment available in almost all laboratories and offices. An example is the xurography technique that uses a cutting plotter machine and adhesive vinyl films to generate the master moulds to fabricate microfluidic channels. In this review, we present a selection of the most recent lithographic and non-lithographic low-cost techniques to fabricate microfluidic structures, focused on the features and limitations of each technique. Only microfabrication methods that do not require the use of cleanrooms are considered. Additionally, potential applications of these microfluidic devices in biomedical engineering are presented with some illustrative examples.

1. Introduction

In the last 20 years, microfabrication technologies have become an important research area for microfluidic applications in different scientific and industrial areas (Stone et al., 2004; Hansen and Quake, 2003; Zare and Kim, 2010), from environment (Bridle et al., 2014; Mehta et al., 2006), to pharmaceutics (Postier et al., 2008) or biomedical engineering (Ruffien-Ciszak et al., 2008; Fujii, 2002; Sackmann et al., 2014). In particular, biomedical microsystem technologies for diagnosis applications have an extremely enhanced potential for being used as point-of-care devices (Kopp et al., 1997; Urban, 2009; Ribeiro et al., 2005). These systems typically feature high analytical performance, high system integration, improved potential for automation and control, small volume of analytes and reagents, safety, reduced cost, greater sensitivity, disposability and shorter analysis times, when compared to the conventional size systems (Urban, 2009; Figeys and Pinto, 2000; Whitesides, 2006; Haeberle and Zengerle, 2007; Squires and Quake, 2005; Lauks, 1998; Melin and Quake, 2007; Ziaie et al., 2004). Manz et al. (1990) proposed the first miniaturised total analysis system (TAS), able to automatically perform the sampling, transport, chromatographic separations and detection of samples at a microscale level. Since then, many authors have proposed micrototal analysis systems for different applications and have explored different microfabrication techniques.

In the 90s decade, photolithography and micromachining in silicon were the most popular microfabrication techniques due to their

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vast use for microelectronics integrated circuits and microelectromechanical systems (MEMS). This popularity leads to adapt them to the fabrication of microstructures on glass and oxidised silicon (Whitesides et al., 2001; Terry et al., 1979; Wilding et al., 1994) for biological and biomedical applications, such as deoxyribonucleic acid (DNA) arrays, cells, proteins and clinical diagnostics studies (Zare and Kim, 2010; Westin et al., 2000; Schena et al., 1995; Chen et al., 1998; Duffy et al., 1998; Rhee et al., 2005; Taylor et al., 2003; Qin et al., 2010; Mitra and Chakraborty, 2011). Although glass and silicon technologies offer high precision, the fabrication methods are complex, time consuming and costly, since the use of cleanroom facilities is required each time a device is made (Ziaie et al., 2004; Duffy et al., 1998; Patel et al., 2008). Additionally, glass and silicon are fragile and too expensive materials for disposable devices. It is important to notice that silicon is optically opaque and semiconductor and, consequently, inappropriate for certain types of separation and detection mechanisms (with risk of sample carry-over and cross contamination) (Duffy et al., 1998). These limitations increased the research into alternative materials (Patel et al., 2008). Therefore, in the second half of the 90's decade, polymers started to be used for microfluidic structures fabrication (Fujii, 2002; Whitesides et al., 2001; Duffy et al., 1998; Patel et al., 2008; Pinto et al., 2014; Xia et al., 1997), and emerged as an attractive alternative to glass and silicon, due to their low-cost, wide range of mechanical and chemical properties, flexibility and easy processing (Whitesides, 2006; Patel et al., 2008; Pinto et al., 2014; Wong and Ho, 2009). The fabrication process using polymers is based on replication, which makes this process to be faster and less expensive when compared with the technique used with glass and silicon (Duffy et al., 1998; McCormick et al., 1997; Becker and Locascio, 2002). The most popular polymers for microfluidic systems are poly(dimethylsiloxane) (PDMS), poly(methyl methacrylate) (PMMA), high-density polyethylene (HDPE), low-density polyethylene (LDPE), polyamide 6 and SU-8 (Ziaie et al., 2004; Becker and Locascio, 2002).

Photolithography is a highly developed technology for micropatterning and microfabrication (Levinson, 2005; Bhushan, 2007). The photolithography process begins with producing a mask (typically a chromium pattern layer on a glass plate), and covering the substrate (such as silicon, glass or GaAs) wictive polymer – photoresist. Ultraviolet light is then emitted through the mask onto the photoresist and it is developed, transferring the mask pattern to the photoresist layer above the substrate (Bhushan, 2007; Fraden, 2010). Two different kinds of photoresist are available: positive and negative. In a positive resist, the UV-exposed areas are dissolved in the subsequent development stage, whereas in a negative photoresist, the exposed areas remain intact after development (Bhushan, 2007). Although photolithography is by far the most common lithography technique in microelectronic fabrication, electron-beam (Broers et al., 1996) and X-ray lithography (Heuberger, 1988) are two other alternatives which have attracted considerable attention in the MEMS and high resolution nanofabrication areas. However, photolithography, electron-beam and X-ray lithography techniques have high cost, necessity of cleanrooms that increase the fabrication cost, limited control over surface properties, long time from the design to the prototype and inaccessible techniques to the majority of the biologists. Those features are slowing down the interest of the industrial community to commercialise these kinds of devices, and consequently, are limiting the use of this technology in biological and biomedical applications (Ziaie et al., 2004; Whitesides et al., 2001; Bhushan, 2007). Hence, it is crucial to develop low-cost alternatives for the fabrication of microstructures, avoiding the use of cleanroom facilities. A large number of research groups that are developing new microdevices do not have expensive cleanroom facilities and, as a result, do not have equipment frequently used in photolithography such as the mask aligner. This review focus on the selection of the most recent lithographic and non-lithographic low-cost techniques to fabricate microfluidic structures, where special attention is devoted on the features and limitations of each technique. Note that, in this review only microfabrication methods that do not require the use of cleanrooms are considered. Methods that involve cleanroom facilities have been reviewed elsewhere (Whitesides et al., 2001; Rodrigue et al., 2015; Kim et al., 2008; Rogers and Nuzzo, 2005; Xia and Whitesides, 1998). Additionally, this review shows current and potential applications of these microfluidic devices in biomedical engineering.

2. Soft lithography

One of the most popular methods to fabricate biomedical microfluidic devices is by using soft lithography techniques (Whitesides et al., 2001; Duffy et al., 1998; Kim et al., 2008; Pinho et al., 2013; Faustino et al., 2014; Feng and Tsai, 2010; Abdelgawad et al., 2008; Rodrigues et al., in press-a), with organic and polymeric materials (Whitesides et al., 2001; Patel et al., 2008; Pinto et al., 2014; Becker and Locascio, 2002). The term “soft lithography” was first referred in 1998 (Xia and Whitesides, 1998), and this technique is based on printing and replica moulding using elastomeric (mechanically soft) materials photomasks, stamps or moulds with the patterns of interest (Ziaie et al., 2004; Whitesides et al., 2001; Abdelgawad et al., 2008; Anderson et al., 2000; McDonald and Whitesides, 2002) for the fabrication of microfluidic devices. Soft lithography represents a conceptually different approach to rapid and low-cost prototyping of various types of both microscale and nanoscale structures and devices on planar, curved, flexible and soft substrates (Qin et al., 2010). It allows complex biochemical patterning (Whitesides et al., 2001; Chen et al., 1997; Bernard et al., 1998), in opposition to the photolithography, a high cost microfabrication technology based, mainly, on glass and silicon substrates through relevant techniques such as patterning, etching, bonding and integration (Chen et al., 1997).

The soft lithography technology overcomes the main photolithography limitations usually found for biological and biomedical applications. Soft lithography allows the control of the molecular structure of the surfaces, the micropatterning of complex molecules and the fabrication of microfluidics channel structures (Whitesides et al., 2001; Xia et al., 1997). Additionally, the use of elastomeric materials allows the micropatterned surface to come into conformal contact with the surfaces over large areas, replicating the three dimensional topography of a patterned, solid surface by replica moulding (which is successful even with features that are only one nanometre, as achieved by Whitesides et al. (2001), Gates and Whitesides (2003), Gates et al. (2004), Gates (2005), Abdelgawad et al. (2008), Anderson et al. (2000), Gates and Whitesides (2003), Gates et al. (2004), Gates (2005) and Fiorini and Chiu (2005). Since the typical moulds are rigid, the use of an elastomer enables an easy detachment of the mould and replica. Polymeric stamps can also be used as moulds for fabrication with rigid materials that cannot be moulded and separated on conventional, brittle moulds. One of the main advantages of soft lithography is the easy bonding of the moulds to polymeric, elastomeric or glass substrates, regarding the sealing process, which can be reversible or irreversible (Becker and Locascio, 2002).

PDMS has become popular among researchers because it has many favourable properties for prototypes fabrication: the material is inexpensive, optically clear (transparency to visible light makes it compatible with optical detection systems), and biocompatible; its moulding procedure is safe and easy to learn; and its flexibility allows the integration of elastomeric actuators and optical elements into devices (Wong and Ho, 2009; McDonald and Whitesides, 2002; Fiorini and Chiu, 2005). Additionally, PDMS has