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Hot embossed polyethylene through-hole chips for bead-based microfluidic devices

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ABSTRACT

Over the past decade, there has been a growth of interest in the translation of microfluidic systems into real-world clinical practice, especially for use in point-of-care or near patient settings. While initial fabrication advances in microfluidics involved mainly the etching of silicon and glass, the economics of scaling of these materials is not amendable for point-of-care usage where single-test applications force cost considerations to be kept low and throughput high. As such, materials base more consistent with point-of-care needs is required. In this manuscript, the fabrication of a hot embossed, through-hole low-density polyethylene ensembles derived from an anisotropically etched silicon wafer is discussed. This semi-opaque polymer that can be easily sterilized and recycled provides low background noise for fluorescence measurements and yields more affordable cost than other thermoplastics commonly used for microfluidic applications such as cyclic olefin copolymer (COC). To fabrication through-hole microchips from this alternative material for microfluidics, a fabrication technique that uses a high-temperature, high-pressure resistant mold is described. This aluminum-based epoxy mold, serving as the positive master mold for embossing, is casted over etched arrays of pyramidal pits in a silicon wafer. Methods of surface treatment of the wafer prior to casting and PDMS casting of the epoxy are discussed to preserve the silicon wafer for future use. Changes in the thickness of polyethylene are observed for varying embossing temperatures. The methodology described herein can quickly fabricate 20 disposable, single use chips in less than 30 min with the ability to scale up 4 times by using multiple molds simultaneously. When coupled as a platform supporting porous bead sensors, as in the recently developed Programmable Bio-Nano-Chip, this bead chip system can achieve limits of detection, for the cardiac biomarker C-reactive protein, of 0.3 ng/mL, thereby demonstrating that the approach is compatible with high performance, real-world clinical measurements in the context of point-of-care testing.

1. Introduction

In the past few decades, microfluidic lab-on-a-chip (LOC) devices have shown potential for use in a wide range of clinical and bioagent detection applications (Bange et al., 2005; Haeberle and Zengerle, 2007). In contrast to existing detection approaches that are time-consuming, expensive, and confined to the laboratory, LOC devices offer potential to house tests that can be completed with low cost and low sample volume requirements, as well as rapid turnaround of results, often in multiplexed format as is desirable for use with near patient testing (Chin et al., 2007; Vilkner et al., 2004; Weigl et al., 2008). Furthermore, these sensitive early disease detection devices, have the potential to improve health and open up more effective therapeutic options for the management of the care of patients (Gubala et al., 2011; Rivet et al., 2011).

Most LOC devices, traditionally composed of glass or silicon, are microfabricated using MEMS technologies, such as photolithography and anisotropic etching to produce simple, highly reproducible, passive channels and features (Zhao and Bau, 2008, 2009). However, long fabrication times for silicon and opaque optical properties of this semiconductor have limited its widespread use (Chin et al., 2012). Moreover, while glass offers optical transparency possibilities for a wide spectral range, highly corrosive and toxic chemicals used in the processing of glass limit its widespread use by the research and in vitro diagnostics communities (Lim and Zhang, 2007). However, with the advent of soft lithography methodologies to produce LOC devices composed of polydimethylsiloxane (PDMS), active LOC components such as

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valves and pumps have been developed and yield enhanced LOC devices' mechanical functionality as well as allow for complex logic and scaled operations under low sample volumes (Hashimoto et al., 2006; Walker and Beebe, 2002a). While PDMS offers biocompatibility and the diffusion of gases, it is limited in its capacity to yield scalability due to slow fabrication times and high costs, and lack of mechanical properties of typical disposable medical device units (Jrbe et al., 1988; Sramka et al., 1988; Sramkova and Kotrly, 1988). Furthermore, although there are many advantages of these materials in research settings, they are limited in most cases to laboratory and research settings due to long production times and high manufacturability costs (Arsenault et al., 2009; Kim et al., 2009a).

With these considerations in mind, a number of groups have started to develop biosensor devices that are amenable to distribution in point-of-care settings (Arsenault et al., 2009; Liu et al., 2007). These important advances rely on a combination of low-cost raw materials that are integrated with detection modalities so as to yield disposable devices where each device ideally costs less than $1 (Chin et al., 2007). For example, instrument-free devices using paper-based microfluidics have recently exploited the low costs of paper as well as capillary action due to the material's inherent porous structure with the aim to develop disposable, easy to use devices (Lau and Liu, 2007; Li et al., 2011; Ng et al., 2008; Phillips et al., 1988). With the ease of disposability through incineration, these colorimetric-based devices can be analyzed using mobile phones, which is increasingly beneficial in resource poor environments where distance and cost are barriers for diagnostic devices (Zhang et al., 2006). To date these paper-based devices have focused on semi-quantitative results interpreted by human eyesight and in some cases evaluated by remote imaging systems. These devices have yet to be found suitable for the rigorous needs of traditional clinical diagnostics (Prasad et al., 1988; Zhang et al., 2006).

With these considerations in mind, there has recently been a strong focus of the medical microdevice research sectors to explore thermoset polymers as potential materials for LOC devices for the use at the point-of-care (Liu et al., 1987b; Wang et al., 1989). These polymer materials offer many appealing benefits including low cost, scalability, disposability, quick production times, and strong optical performances (Liu et al., 2006; Yuan et al., 1989). In the fabrication of such devices, a mold containing desired features is either embossed into or injected with thermoset polymers at a temperature above the polymer's glass transition temperature. Following a demolding phase to cool the mold to a temperature below the glass transition temperature, the part is removed from the mold (Becker and Gartner, 2000). Thermoplastic parts can achieve resolutions down to the sub-microns (Kurzeja et al., 1986; Lin et al., 1987; Liu et al., 1984b). While these techniques are initially and extremely expensive due to the high start up costs and long development times associated with the machine and mold, typically produced through micromilling, the low cost of thermoplastics and economics of scaling allow for a rapid decrease in cost per unit with increasing quantities produced (Wang et al., 1989). To help with these barriers, several groups have developed low-cost alternatives for such fabrication tools (Chung et al., 1987; Liu et al., 1984a).

Thermoset polymer-based devices have successfully been developed for the use in several microfluidic-based devices. For example, work by Sia et al. (2004), Sramkova and Kotrly (1988) have developed integrated plastic devices that have moved into real world practice. Likewise, hot embossed devices, based on the thermoplastic cyclic polyolefin, have been developed for the extraction of DNA and for the detection of cardiac biomarkers in human sera (Garstecki et al., 2006a; Gitlin et al., 2006a). Furthermore, the adsorption properties of thermoplastics have been harnessed to immobilize antibodies onto polystyrene devices (Liu et al., 2004). Similarly, surface treatment of thermoplastic can facilitate bonding and modify hydrophilic properties. Furthermore, chemical treatment of non-adsorbing surfaces of thermoplastics allows for the functionalization of antibodies (Gubala et al., 2011; Lin et al., 1992; Ogle et al., 1988). These chemical treatments show promise for a wide range of plastic-based devices.

Furthermore, PMMA has also been harnessed for the surface immobilization of antibodies in capillary flow-based devices. Application of a sol–gel technology allows for a surface coating that facilitates antibody bonding (Chin et al., 2007). Additionally, thermoplastic-based devices, used to culture cells, reveal both strong cell attachment and growth to PMMA surfaces (Liu et al., 1987a). Likewise, surface immobilization onto a plastics show the potential of plastic-based biochips as replacements for large equipments such as liquid chromatography for the detection of anesthetics (Jokerst et al., 2011). Work completed by Klapperich et al. has demonstrated the application of plastic microfabrication to create devices with potential global applications for polymerase chain reactions. These developments reveal the capability of these plastics devices to service point-of-care DNA testing (Cao et al., 2011, 2012).

Recently, there has been much interest in the use of beads as highly sensitive sensing elements in microfluidics. For example, Walt (2010a, 2010b) and coworkers have utilized optical fibers with microarrays of polymer beads for the detection of vapors, representative of the olfactory glands. Ng et al. (2008) have demonstrated a chip containing micropillars that hold a microarray of polymer beads for the detection of DNA. This device demonstrates the rapid detection of multiple bacterial species and nucleotides in less than 10 min. Furthermore, these sensors can be multiplexed to detect multiple DNA probes and proteins simultaneously (Konry et al., 2009). Thompson and Bau (2012) have developed a model for the temporal and spatial distribution of captured analytes in porous beads. These models agree well with confocal imaging. Similarly, our group has shown, through simulations and experimental evidence, the preponderance of porous beads as highly sensitive sensing elements due to the existence of internal convection inside porous beads (Chou et al., 2012). These bead-based devices have shown potential as highly sensitive, robust sensing elements for rapid detection of biological agents (Derveaux et al., 2008).

Over the past decade, our laboratory has sustained efforts to design, fabricate and validate in clinical settings for various health conditions a platform technology described as a programmable bio-nano-chip (p-BNC) system (Kim et al., 2009b; Nguyen et al., 2009; Zhao and Bau, 2010). This modular platform is programmable in the sense that it can move in an agile way from one biomarker to the next through the insertion of molecular level code. The bio element refers to the biological aspects of the various disease and health conditions that may be monitored with this system. The nano terminology refers to the miniaturization that is embodied with nanonets to capture with high efficiency the critical biomarkers as well as quantum particles that can be used to enhance signaling. Finally, the chip terminology refers to the capacity to use microfabrication capabilities to produce the devices at scale. With this p-BNC system we have developed a flow through, pressure-driven ensemble consisting of an array of highly sensitive agarose beads resting in anisotropically etched silicon wells. This unique flow through design enables convection-driven internal transport within the situated porous beads. Versus lateral flow over designs, this design allows for shorter diffusion distances which allow for higher fractional capture efficiencies.