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LARGE-SCALE FABRICATION OF MICROFLUIDIC CHIPS WITH THREE-DIMENSIONAL MICROSTRUCTURES FOR POINT OF CARE APPLICATION

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ABSTRACT

This paper provides new insights into the process of rapid, low-cost and large-scale fabrication of polymer microfluidic chips containing three-dimensional microstructures using in point of care devices, for applications such as detection of pathogens via a molecular diagnostic method, namely polymerase chain reaction (PCR). The details of fabrication methods are described. Do's and don'ts are given to help both the experimentalist in labs and in industrial production to avoid doom fabrication issues.

KEYWORDS: polymer, microfluidics, three-dimensional microstructures, polymerase chain reaction (PCR)

INTRODUCTION

Lab-on-a-chip technology for biochemical applications such as bio-sensing, pathogen detection and safety control has grown tremendously in recent years. Most of the applications are fluorescent bases, thus require the utilization of optical materials for making the chip part. Materials for optical measurement need to satisfy strict criteria, namely low surface roughness and high transparency with visible and UV lights. In this scenario, the microfabrication technique is mostly applied to glass and fused silica (silicon is not in this catalogue since it is not transparent with visible and UV lights). Nevertheless, those materials are expensive, difficult to handle not only on an industrial scale but also on a small scale such as for university laboratories. In the last 20 years, due to the fast development of material science, polymers that meet the optical demands are made available, for instances Cyclo-olefin Polymer (COP) and Cyclic Olefin Copolymer (COC), Polystyrenes (PS), Poly(methyl methacrylate), etc. Micro-, nano-fluidic devices with 1-D channels have been fabricated using these materials for bio-physical measurement and sensing [1,2]. Making these thermoplastic polymers into three-dimensional (3-D) microstructures with low surface roughness and high production efficiency (high reproducibility) is, however, still a challenging task, especially for large-scale and low-cost application. Previously, our group has shown some attempts to produce 3-D structures with COC and PS using for biosensing and pathogen detections such as the works of Tran and Kant [3,4]. However, up-to-now, there have been no systematic reports or protocols that fully describe both the fabrication steps and the production efficiency, which can aid for massive production on an industrial scale. In this report, we present a complete and systematic protocol of a large-scale and highly reproducible technique that is employed for rapid fabrication of 3D micro-arrays optical structures using quick pathogen detection devices. This protocol, at large, can be extended and applicable to rapidly fabricate any other 3D microstructures (on and off-chip) down to the order of 10 microns.

EXPERIMENTS AND RESULTS

Because the material is thermoplastic, the industrial-scale production technique chosen is polymer injection moulding. The fabrication thereby includes three main steps: (i) Design the mould insert (also called the shim) using computer-aided design (CAD) (Inventor 2018), simulation (Cimatron E13), (Fig. 1). (ii) Shim fabrication by micro-milling and polishing (Fig. 2 and 3). (iii) Polymer injection moulding (Victory 80/45 Tech, Austria). Notes and remarks for avoiding mistakes in the fabrication processes are provided (Fig. 4 and 5). As a proof of bio-applications, after the fabrication step, the resulting 3D micro-arrays of optical structures are used in a multiplexed solid-phase PCR to detect and differentiate *Salmonella* Typhimurium and *Salmonella* Enteritidis (Fig. 6).

REFERENCES

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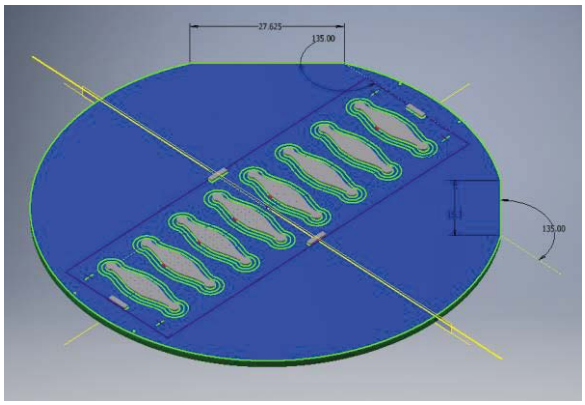

Figure 1:The CAD design of the mould insert (diameter = 85 mm). Number in the figure is in mm unit.

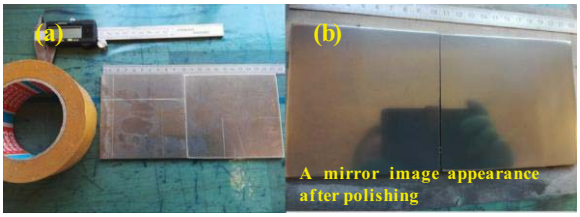

Figure 2: The Al-plate before (a) and after (b) polishing

Figure 3: Digital pictures of (a) Milling machine. (b) Attached double-sided tapes on the backside of the Al-plate to immobilize it on the milling stage. (b) Cooling oil from Wurth, Germany. (c) Milling stage where the Al-plate is attached and the cooling oil is applied on the Al-plate surface. (e) Applying the polishing paste after bulk milling using Autosol ALUMINUM polishing paste and cleanroom paper.

Acknowledgements

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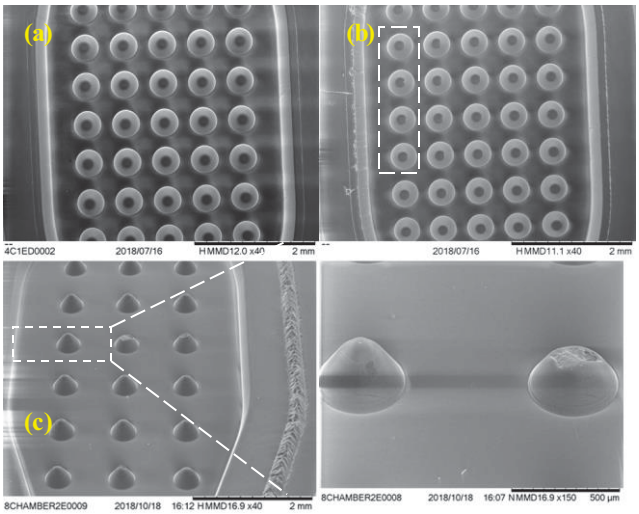

Figure 4: SEM images of (a) the good 3-D microstructures fabricated by polymer injection moulding using milling shim where the washing step is applied with enough washing time. (b) Defected structures in case the shim did not receive enough washing time (less than 30 mins). (c) Defected structures when the shim did not receive a washing step.

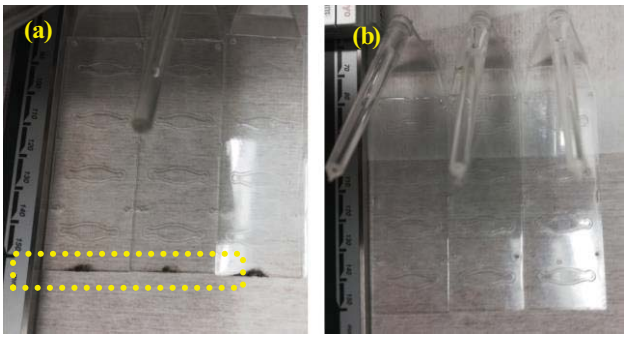

Figure 5: Chips with (a) and without (b) burning at the end due to Diesel effect.

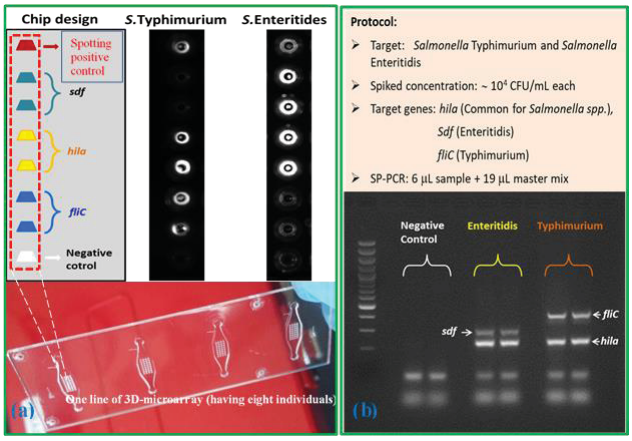

Figure 6: (a) DNA molecular binding dyes are spotted on the top of the fabricated 3D microstructures and fluorescent images are captured from the fluorescent scanner BioAnalyzer 4F/4S (LaVisionBiotec GmbH, Bielefeld, Germany) for multiplexed SP-PCR to detect and differenciate S. Typhimurium and S. Enteritidis. (b) The gel image of liquid phase PCR products.