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REALIZATION AND TESTING OF LAB-ON-CHIP FOR HUMAN LUNG REPLICATION

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ABSTRACT

This research realised 3D constructs so called lab-on-chip as pathways to study human cell under a controlled environment. The chip is a sandwich of two microchannels with microporous membrane in between to mimic human lung system. The challenge is the fabrication of each micro part and assembles them becoming a functional micro system. Firstly, the session was preceded by realization of 20mm x 0.5mm x 0.3mm (length x width x thickness) channels. Later on, porous membrane with size of 100µm x 100µm arranged as arrays were also realised using micro milling apparatus. Eventually, the system was tested by employing 300ml/h propanol and water in each channel. The diffusion of propanol into water channel was validated by gas chromatography (GC) apparatus to validate the functionality of the system.

Keywords: lab-on-chip, lung system, micro-parts, micro-assembling.

INTRODUCTION

Study of lab-on-chip is consistently increased during the last two decades. The fact that medical and pharmacy industries were studying toxicology and therapeutic effect become the motivation [1]. It is reported that duration of 6-8 years is needed to test a new pharmaceutical product). Additionally, 1.3-1.7 billion USD fund is needed to finance the testing process. Generally, only one product that positively resulted from 5,000-10,000 proposed product. It is also reported that animal testing is one step that requires the most resources fund. However, the results from animal testing have failure in predicting the result since it could not fully replicate human system [2].

Specifically, organ-on-chip technology has played important role in physiology study that enables researcher to model human diseases in-vitro. This method was evident by combining tissue engineering and microfluidic technology [3]. Nowadays, microfabrication technology enables us to realize controlled microfluidic environment to be applied as replication of structure and mechanism of an organ [4]. Organ-on-chip was introduced by Ingber and Huh that member of Wyss Institute for Biologically Inspired Engineering. They demonstrated lung-on-chip to replicate the phenomenon of human cell that responded to bacteria. This finding were interpreted as mechanical response that never been detected conventionally in 2 or 3 dimensional cell culture [5, 6]. A more accurate system is being researched in order to successfully mimic human lung system.

This research focuses on the design and realization of lab-on-chip system to using PDMS material. The PDMS microchannel and microporouss membrane were carefully fabricated using micromolding technique. Micromilling apparatus that developed in Department of Mechanical Engineering UI [7] realised microbar with dimension of 102.9µm x 101.9µm.

MATERIAL AND METHOD

Fabrication of Porous Membrane

A mold consist of an array of microbars with dimension of 100µm x 100µm x 80 µm was fabricated using DTMUI micromilling apparatus. Later on, PDMS Sylgard 184 was poured onto microbars mold and spincoated for 30 seconds in 2, 500 RPM. The mixing was then placed onto oven for 5 minutes at temperature of 80^{o}C to be crosslinked further.

Fabrication of Microchannel

A block of aluminium 7075 with dimension of 20mm x 11.5mm x 10 mm was prepared as channel mold. A conventional milling was used to form channel with dimension of 2mm x 0.5mm x 0.1mm. Polydimethylsiloxane (PDMS) Sylgard 184 Elastomer Kit from Dow Corning solution was used. A 1:5 weight ratio of curing agent was mixed to form a stiff and colorless geometry to follow the aluminum mold. The mold with PDMS was placed in an oven for 45 minutes in temperature of 80^{o}C to quicken the crosslinking process.

System Assembling

PDMS porous membrane was placed between two PDMS microchannel parts. The alignment was utilized digital Dynolite microscope. Outer parts were housed by acrylic plates as fixture and syringe inlet. Terumo syringe pump TE311 was used to inflow the propanol and water into the lab-on-chip.

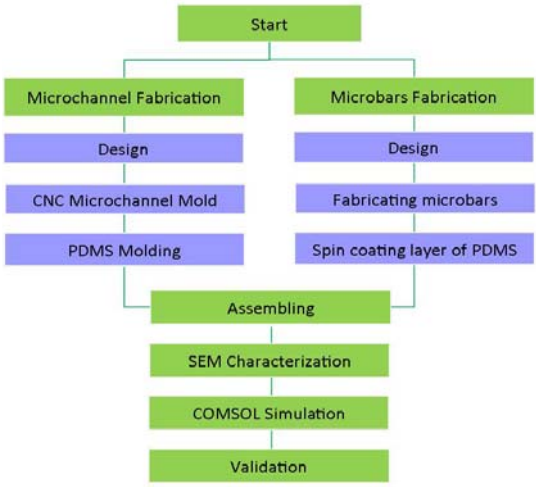

Figure-1. Process Workflow.

Geometric Characterization of Lab-on-Chip

Optical microscopy was used to investigate the microstructure of realised 3D microchannels. Olympus AX70 optical microscope equipped with Olympus C-5060 Camera and image processing software was utilized. Moreover, the texture and mold surface was measured by Accretech Surfcom 2900SD3. Ultimately, Scanning Electron Microscope (SEM) was used to characterized microbars and realised porous.

Functional Testing and Mass Transfer Validation

Validation step was taken place to confirm that the lab-on-chip system function as it aimed with a good fitting and no leakage. Firstly, diffusion of propanol into water was modeled in COMSOL environment. Secondly, a portion of sample from propanol outlet was measured using Agilent 7890A Gas Chromatography System.

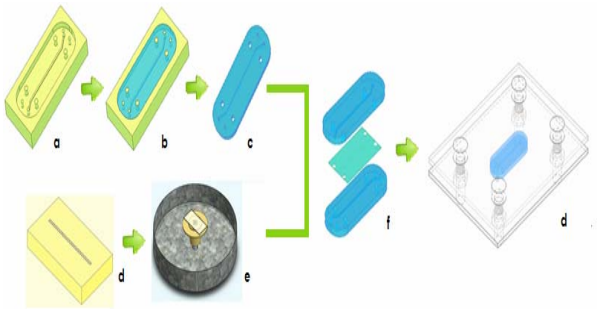

Figure-2. Assembling of porous membrane and microchannels.

RESULTS AND DISCUSSIONS

Geometrical Characterization of Lab-on-Chip Microchannel

Realised microchannel mould has width of 477.2µm and 482.6µm (top and bottom part). Figure-3 depicts PDMS microchannel with dual flows indicated by red and blue liquid. Furthermore, the product of PDMS has 491.6 µm and 488.6µm. Keep in mind that the width was designed at dimension of 500µm. This indicates to improve the mould in order to have more accurate product dimension. Additionally, the roughness of the mould was 0.8924µm and resulted a product with roughness of 0.4993µm.

The length showed of 1.927mm and 1.829mm for mould and product, respectively. The depth that measured has 105.26 µm and 108.52µm for mould and product, respectively. Meanwhile the aimed dimensions are at 2mm and 100µm for length and thickness respectively. A mismatch of 8% was calculated between realised products with its design.

Porous membrane

In order to create porous membrane, an array of microbars was realised. The milling process was done by using micromilling apparatus that developed at our department. Tools that used were flat end mill with diameter of 2mm, 0.2mm and 0.1mm. Two kinds of arrays were formed which are 1x26 and 2x39 (see Figures 4a and 4c).

Figure-3 depicts the SEM result for both arrays and it can be indicated that the bar contour were rather different. Microbars for 1x26 array has parallel shape from bottom to the top. The realised dimension is 102.9µm x 102.0µm with a depth of 40µm. Spindle speed was set at 70,000 with feed rate of 20µm. On the other hand, microbars for 2x39 array has asymmetric shape from bottom end to upper part. The bottom end has dimension of 125.8µm x 122.5µm while upper part has tipped to 80.7µm x 77.7µm. This asymmetric was due to wear of the tools. It can be hindered by using 2 tools with size of 0.1mm. The tools that used was also crunched the corner part of the bars.

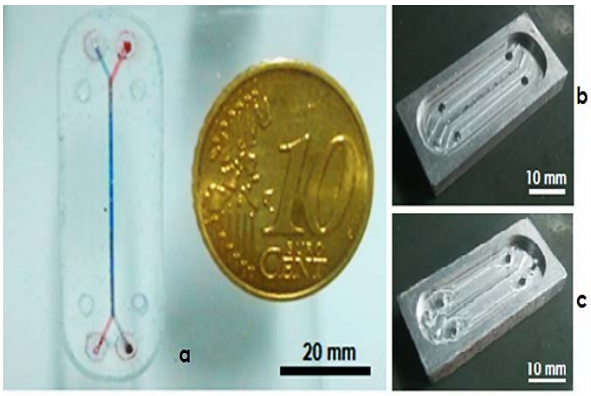

Figure-3. a) Realised PDMS product b) Bottom Mold and c) Top Mold.

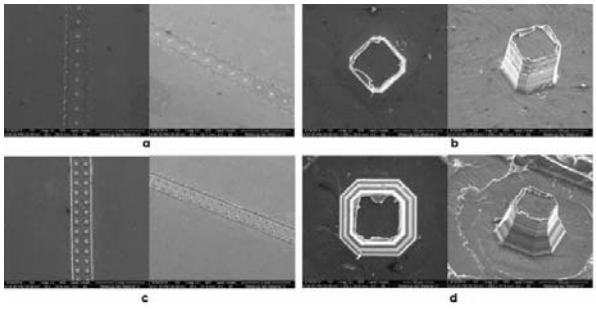

Figure-4. SEM results on Microbars a) 1x26 array b) microbar c) 2x39 arrays and d) microbar.

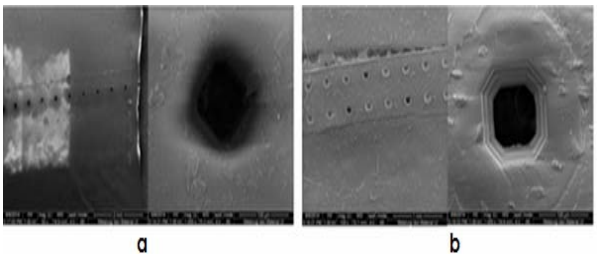

Figure-5. SEM Result of porous membrane a**)** 1x26 array and b**)** 2x39 array.

Later on, Figure-5 depicts the porous that realised using the microbars as mould. It can be seen that membrane from 1x26 arrays has a parallel shape better than 2x39 arrays. The dimension that resulted is 106.8µm x 103.7µm and 85.7µm x 77.7µm for 1x26 and 2x39 arrays, respectively. The dimension that measured was upper part as for 2x39 array microbar although the bottom end has 126.5µm x 124.4µm dimension. The mismatch between porous as designed versus realised was at 2% for 1x26 array, whereas 25% mismatch was found for 2x39 array.

Functional Testing and Mass Transfer Validation

A simple diffusion simulation was introduced at COMSOL environment to emulate the behavior of microflow in our lab-on-chip. Here, propanol and water were chosen as two mixing fluidic. However, the observation was only done in propanol regime. In order to know the effectiveness of our membrane, four kind of simulation model were employed which are:

a) flow without membrane between both channel
b) flow with membrane using 1x26 array porous
c) flow with membrane using 2x39 array porous
d) flow with membrane without any porous.

It is expected that the concentration of propanol without membrane (condition a) should have the lowest concentration among four condition of simulation since propanol will diffuse out to water regime. On the other hand, the highest concentration should be addressed to flow propanol with membrane without any porous (condition d). Furthermore, propanol flow with membrane 1x26 array porous shall have higher concentration compare to that 2x39, since the mixing zone is lesser.

Figure-6 depicts the simulation of four conditions in COMSOL environment. The diffusion coefficient was set to $1.12x10^{-9}$ m^2/s and volumetric flow is 300mL/h. Figure-6a confirms that the propanol in outlet has the lowest concentration indicated by its blue colour. Moreover, Figure-6d shows highest concentration of propanol outlet since no mixing is evident.

Figure-7 indicates a similar trend between experimental and simulation environment result although both arrays are likely the same (less than 1%). However, it also can be indicated from the simulation that the difference between both arrays shall only be 7% difference. The further observation shows that not all porous were perfectly holed. Additionally, the simulation without any porous confirms that the experimental result has 3% error.

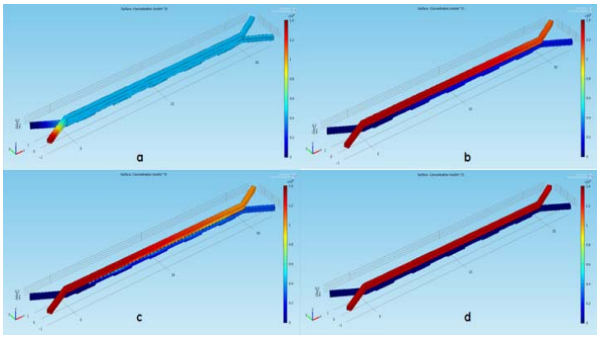

Figure-6. COMSOL simulation a) without membrane; b) using membrane with 1x26 array porous; c) using membrane with 2x39 array porous; d) using membrane without any porous.

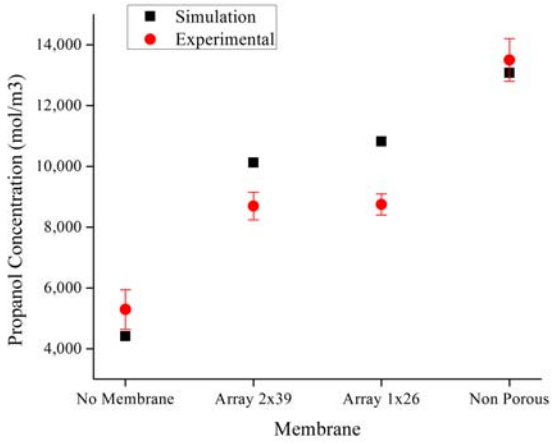

Figure-7. Mixing Concentration of Propanol from Simulation and Experimental Result.

CONCLUSIONS

All micropart of lung-on-chip have been designed, fabricated and well assembled. The mismatch

between designed and realised product are in the range of 3-8%. Furthermore, the mismatch in flow diffusion is in the range of 15% which indicates that diffusion coefficient should be corrected. However, the results give a clear indication to develop the product as lung-on-chip.

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