A Low Temperature Co-Fired Ceramic Mesofluidic Separator

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Abstract. A 3-dimensional mesofluidic separator has been successfully designed and fabricated using a low-temperature co-fired-ceramic (LTCC) technology. This mesofluidic separator consists of several vertical micro-channels and horizontal distribution cavities to create the velocity increase before entering a bent microchannel. The centrifugal force created by the bent microchannel further increases the fluid velocity to enhance the plasma skimming effect. Separation of the white and red blood cells in anti-coagulated blood has been demonstrated using this mesofluidic separator.

I. Introduction

Microfluidic and mesofluidic analytical systems are becoming very popular in chemical and biomedical applications due to the need of small volume reagents, small waste and short reaction time. Most of these systems are based on silicon, glass, polymethylmethacrylate (PMMA) or polydimethysiloxane (PDMS) substrates. A true 3-dimensional microfluidic structure cannot be easily implemented using these substrates due either to the process limitations or material properties. The use of a low-temperature co-fired ceramic (LTCC) technology for microfluidic devices allows for the realization of multiple 3-dimensional microchannels, a feature not easily attainable in other MEMS technology [1-2]. Furthermore, electrically conducting paths, if needed, can be integrated into these microchannels.

Many clinical chemistry tests are performed on cell-free plasma or serum as the blood cells yield measurement biases to make reproducible results difficult. The conventional blood separation technique is by centrifugation and membrane filtration. However, most centrifugation devices are not portable due to their size and the requirement of a stable separation platform. Microfabricated devices have been used in blood separation [3-4]. The use of a filtration system requires a high injection pressure and these filters may be clogged [3]. Polymer-based (PMMA) microchannel bends were used in blood separation [4]. This separation was based on the centrifugal force field created by the bent microchannel and the plasma skimming [4]. Plasma skimming occurs in bifurcating capillary blood vessels as particles enter the vessels with a higher velocity.

In this study, a 3-dimensional mesofluidic separator has been successfully designed and fabricated using a low-temperature cofired-ceramic (LTCC) technology.

2. Design and Simulation
The mesofluidic separator consists of a single input port, a horizontal distribution cavity, four vertical channels, a second horizontal distribution cavity, three vertical channels, a third horizontal distribution cavity, two vertical channels, a fourth horizontal distribution cavity, and a single vertical output channels in the last layer as shown in Figure 1. The horizontal distribution cavities in between the vertical channels facilitate microfluidic distribution. The single vertical channel flows into a horizontal channel (y1) that branches into two channels (y2 and x) after a 90° bend as shown in Figure 2. Table 1 lists the design parameters for this separator.

![Figure 1. Conceptual design of the mesofluidic separator](image1)

![Figure 2. Top view of the mesofluidic separator showing the design parameters.](image2)

| Table 1. Design parameters of the mesofluidic separator. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Length (x)     | Width (x)       | Length (y1)     | Width (y1)      | Length (y2)     | Width (y2)      | Outer Radius 1  | Inner Radius 1  | Outer Radius 2  | Inner Radius 2  |
| 14224 µm       | 356 µm          | 6350 µm         | 356 µm          | 10160 µm        | 254 µm          | 1168 µm         | 813 µm          | 3175 µm         | 2921 µm         |
The centrifugal force is defined as $F = \frac{mv^2}{R}$, where $m$ is the mass of the blood cells, $v$ is the velocity of the blood cells crossing the microchannel bend, and $R$ is the radius of the bend. As such, in order to increase the centrifugal force, we need to increase the velocity of the blood and to decrease the radius of the bend. In our design, we further make use of the Bernoulli’s venturi effect to increase the fluid velocity. An increase in fluid velocity occurs simultaneously with decreases in pressure as the fluid flows from larger volume multiple vertical microchannels into a single vertical microchannel. The increase in velocity facilitates plasma skimming effect as the fluid flows into two microchannels with different widths after the bend. Figure 3 shows the ANSYS™ simulation. As can be seen in Figure 3, the velocity of the fluid increases from the inlet, and finally achieves its maximum velocity at the 90°C bend.

![ANSYS simulation of the mesofluidic separator (left: top view, right: cross-sectional view)](image)

**3. Fabrication**

The mesofluidic separator was fabricated by the lamination of 10 individual layers of green tape as shown in Figure 4. Layer 1 is the inlet hole of 2388 µm diameter. Layer 2 consists of 33 punched holes of 152 µm diameter. Layer 3 is the distribution cavity of 2388 µm diameter while layer 4 consists of 3 punched holes of 152 µm diameters. Layer 5 is the distribution cavity of 1780 µm. As can be seen, the diameter of the distribution cavity decreases from 2388 µm to 1220 µm in layer 7. Layer 9 is the microchannel layer.

Ferro A6M tape with a thickness of 0.127 mm was used as the substrate [5]. The tape packed as a roll was slit into a 150 mm x 150 mm squares. Due to the limitation of the punching machine, only 120 mm x 120 mm area of the green tape was used. All the layers were punched individually, using an automatic punching machine. The green tape was mounted on the punch-tooling plate and was held tightly with vacuum as the punching machine punched at the coordinates specified by the punch file. Vias were produced using the 0.1 mm diameter punch, while the cavities were produced using either 0.25 mm or 0.5 mm diameter punches. Registration holes between each layer were produced using the 2.4 mm diameter punch. These registration holes were needed to assure that each layer aligned properly.

First, layers L6 and L7 were aligned using the registration holes and stacked together. Then this stacked layer was aligned and stacked with layers L4 and L5. Next, the resultant stacked layer was aligned with layers L1, L2, L3, and L8. Layers L9 and L10 were stacked separately. Finally, these two stacked layers 1-8 and 9-10 were stacked together after alignment. The entire stack was then ready for lamination. Lamination was performed using an iso-static laminator system at a pressure of 800 psi for 5 minutes at 70°C. The laminated green tape was now ready for firing using a pre-determined firing profile to drive out the organic materials and to form the ceramic structure. After reaching the highest firing temperature of 850°C and holding for 10 minutes, the LTCC stack was...
cooled slowly to room temperature. Figure 5 shows the cross-sectional view of the fabricated mesofluidic separator showing the distribution cavities.

Figure 4. Layout of the 10 layers of the LTCC green tape.

Figure 5. Cross-sectional view of the fabricated mesofluidic separator showing the distribution cavities.

4. Results and Discussion

The mesofluidic separator was used for the blood separation. Figure 6 shows the physical interface between the mesofluidic separator and the inlet. In between the steel inlet port and the LTCC separator is the glass cube with an inlet hole aligned directly on top of the inlet of the separator.

Anti-coagulated blood samples were used in the experiments. The blood sample was injected through a plastic tubing directly into the LTCC separator. After the separation, a Coulter HmX hematology analyzer was used to count the red blood cells (RBCs) and white blood cells (WBCs). Table 2 shows the counts of the RBC and WBC from the x and y2 microchannels.
Table 2. Blood cells Separation Result

|        | WBC | RBC |
|--------|-----|-----|
| y2 channel | 0.9 | 0.8 |
| x channel  | 1.4 | 1.0 |

(unit of WBC is $10^9$ cells / L, unit of RBC is $10^{12}$ cells / L)

Figure 6 shows the mechanical interface between the mesofluidic separator and the inlet.

As can be seen, the separation efficiency of the white blood cells is higher than that of the red blood cells (RBC). The differences in separation efficiency between the WBC and RBC are mainly due to their differences in their cell characteristics. The RBC has a disk shape with a length of 6µm to 8µm and a diameter of 2µm. The density of RBC is 1.09g/ml-1.11g/ml. However, the WBC is spherical in structure with a diameter of 10µm -15µm. The average density of the WBC is 1.08g/ml-1.10g/ml. As such, when the RBC and WBC flow through the 90° bend, the centrifugal force imposes on the WBC is larger than that on the RBC, due to its higher mass. The WBC flows to the outer edge of the bend faster than the RBC. As such, the concentration of the WBC in the y2 channel is much lower than that in the x channel.

The radius of the bend can be decreased to increase the generation of the centrifugal force. Making the width of y2 channel smaller to enhance the plasma skimming effect is another way to increase the separation efficiency. We can also fabricate several micro-bends on the outlet of y2 channel, so the fluid flow out of the y2 channel can be separated several times.

In this study, we demonstrated the feasibility of an LTCC mesofluidic separator for blood separation. The device is small and portable. A small quantity of blood can be separated in a shorter time than the traditional centrifugal separator. This mesofluidic separator can be fabricated in a cartridge form to facilitate automation, a feature essential for commercial applications.

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