HIGH RESOLUTION SIZE BASED MICRO PARTICLE/CELL SEPARATOR WITH TRAPEZOIDAL CROSS SECTION SPIRAL MICROCHANNELS

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ABSTRACT

Particle focusing behavior in a spiral microfluidic channel with trapezoidal cross section is studied in this work. By observing the position of particle stream from both side and top view, combined with numerical simulation of Dean flow field, the force balance conditions within these channels is studied for better understanding of particle focusing mechanism in a spiral inertial microfluidic channel. In the spiral inertial microfluidic channel, modifying channel cross section can lead to a shift in Dean flow field, affecting the particle focusing behavior significantly. Based on this mechanism, particles separation with both high resolution and high throughput is reported.

KEYWORDS

Size Based Sorting, Inertial Focusing, Dean Vortex Trapping, Trapezoidal Cross Section, Spiral channel.

INTRODUCTION

The need for efficient size-based cell separation is often found in various cell-based assays, to isolate a certain sub-population from complex cell mixtures such as blood. Recently, inertial microfluidic devices were explored as a filterless size-based cell fractionation method [1-3]. Here, we introduce a novel inertial microfluidic device design with trapezoidal cross-section, which preserves the principle of separation of typical rectangular cross section microfluidic designs, but with significantly improved separation resolution and throughput. Taking advantage of capturing images of particles position at side view, the forces balance mechanism is discussed under a simulation of Dean flow field both for rectangular and trapezoidal cross section.

THEORY

In a rectangular cross-section spiral channel, Dean vortices are symmetrical in the width direction and particles are mostly focused at the inner side of the curved channel. Particles with diameter/height ratio ≥0.07 normally focus into two streams within the Dean vortex at the top and bottom halves of the channels. With flow rate increasing, the particle focusing position initially moves closer to the inner channel walls due to the increased inertial lift forces, while the centrifugal forces begin to dominate at higher flow rates pushing the particle position away from the inners walls towards the outer wall (Figure 2A). This phenomenon limits the throughput and resolution of particle/cell separation, because the focusing positions of particles with different sizes are close to one another [2]. In trapezoidal cross-section spiral channel, with inner walls shallower than the outer walls, the transition from 'inertial–dominant' to 'Dean–dominant' regime is sudden, therefore the focusing position immediately jumps from the inner half to the outer half of the channel. This is due to the evolution of a strong Dean vortex core skewed towards the outer half of the microchannel (the deep region in Figure 1A), rendering the Dean force field nonlinear. As the inertial lift forces are highly size dependent, particles/cells of different sizes shift from the inertial dominant to Dean dominant regime at different flow rates. Using this principle, particles/cells of different sizes can now be separated with greater spatial resolution than in a traditional rectangular cross-section microchannel.

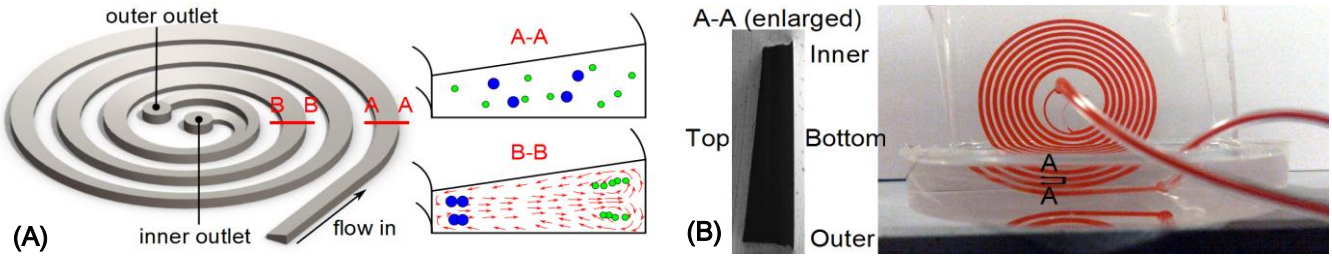

*Figure 1: **(A)** Schematic of trapezoidal cross section channel illustrating the principle of particle focusing and trapping within the Dean vortices. **(B)** An actual PDMS casted trapezoidal cross section spiral microfluidic device with two outlet tubes removed. The cut view of the cross section is shown on left. The radius of the spiral curve varies from 7.5mm to 12.5mm. The inner & outer heights of the channel cross section are 80μm and 130μm. The width of the channel is 600μm.*

EXPERIMENT

Microfluidic channels were cast from a Poly(methyl methacrylate, PMMA) mold made by precision milling process (Whits Technologies, Singapore). The design consists of a single inlet two-outlet spiral channel with multiple loops and curvature radius of ~10mm. The patterns were cast with Sylgard 184 Silicone Elastomer (PDMS) prepolymer mixed in a 10:1 ratio with the curing agent. After curing, the PDMS mold with patterns was peeled plasma bonded to another 3mm thick PDMS layer. Input and output ports were punched prior to bonding. For the observation of particle position from the side, the device is cut along the output section of the channel with ~2mm distance and then a second cast is made by keeping the device vertically to a flat bottle container. Tubings were connected to the ports before the second cast to prevent PDMS mixer flow into the channel.

During testing, microfluidic device was placed on an inverted microscope (Olympus X71) and fluorescence images were captured with Phantom V9.1 camera (Vision Research Inc. USA) near the end of the channel. Input samples were made by diluting 1% solid fluorescent particles (Bangs Laboratories, Inc. USA) of different with DI water and pumped into the channel under different flow rate with NE-1000 syringe pump (New Era Pump Systems, Inc. USA) to observe the focusing positions. For evaluating the separation quality of the device, higher concentration particles of two different sizes were mixed.

RESULTS AND DISCUSSION

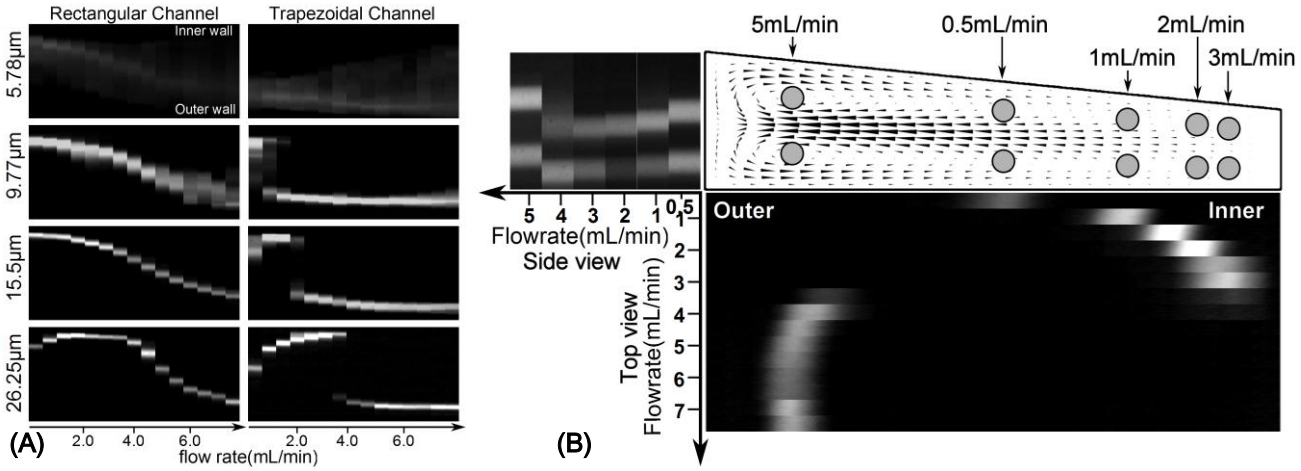

*Figure 2: **(A)** Top view image showing the comparison of fluorescent beads distribution at the outlet of a 80/130µm inner/outer depth, trapezoidal cross section spiral microchannel, and a 80µm height rectangular channel with flow rates ranging from 0.5mL/min to 7.5mL/min. **(B)** CFD Simulation of Dean flow field (inner/outer depth: 80/140µm, width: 600µm, flow rate: 3.5mL/min, channel radius: 7.5mm) combined with 26.25µm fluorescent beads distribution from the top view and the side view, indicating the force balanced position of particles. Black cones indicate the direction and magnitude of Dean flow. Gray circles are positions of 26.25µm beads at typical flow rate from experimental results.*

Figure 2A shows the focusing bands of different sized particles with increasing flow rates as viewed from the top. The result clearly corroborates the separation principle, with particle streams of different sizes shifting from the inner wall (inertial regime) to the outer wall (Dean regime) at different flow rate. For example, with trapezoidal cross-section, at a flow rate of 1.5mL/min, we can separate particles with >15.5µm diameter from smaller ones by collecting inner and outer outlets. In the same channel, increasing the flow rate to 2.5mL/min allows us to separate particles with >26.25µm diameter from smaller ones. In comparison, in rectangular channel, although particles of different sizes tend to focus at different positions of channel at a certain flow rate, the distances between them are minimal and can be blurred if the particle/cell concentration is high, limiting the ability to process high hematocrit cell samples. Figure 3 presents the separation efficiency of two different size particles (16.68µm and 26.9µm) at an optimized flow rate of 3.4mL/min. The purity of both outlets collection are over 96%, while throughputs of 8.85×10^6/min can be reached, which is 1.33% volume to volume concentration (equivalent to hematocrit number in blood samples).

Previously, particles were assumed to focus at the center of channel depth [1-3] in spiral inertial microfluidic channel, since Dean drag force ($F_D \propto U_f^2$, where U_f is the average flow velocity) and inertial force ($F_L \propto U_f^{1.63}$) [3] are dominant at center area of channel cross section, while centrifugal force($F_C \propto U_f^2$) is neglected. But according to our experimental result in Figure 2B, particles are focusing at two different depths. Numerical simulation indicates that the Dean flow field at different flow rates change little in distribution, and the maximum Dean flow velocity is always found at the center in depth direction. At the positions of particle focusing (experimentally found to be between zero Dean line and zero lift force line), F_D is mainly directed towards inner wall, and is also much smaller than maximum Dean force. In such conditions, F_C cannot be neglected.

Figure 4 illustrates the forces act on particles at different positions of channel cross section. At Position #2, all the forces are in the channel width direction, but a slight disturbance along channel depth direction will make F_L to change direction and

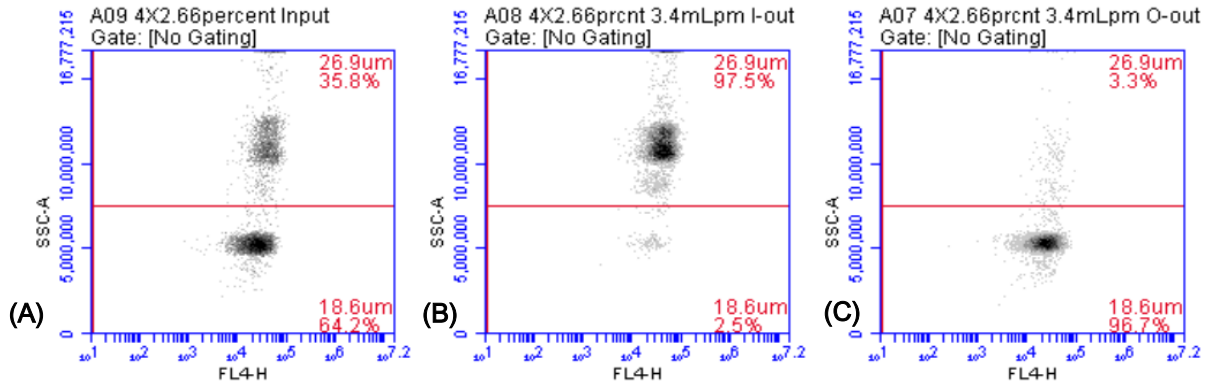

Figure 3: FACS result of particle separation with 80/130μm inner/outer depth, 600μm width trapezoidal cross spiral microchannel at 3.4mL/min flow rate, ***(A)*** *Input with 16.68μm and 26.9μm particle of 0.665% volume to volume concentration(~2.6× 10^6/mL),* ***(B)*** *Inner side output,* ***(C)*** *Outer side output.*

increase in magnitude, which renders this point an unstable balance point. Position #3 is a stable force balance point at low flow rate(0.5mL/min). With the increase of flow rate, F_L grows faster than F_D, particle balance point will have to move towards the top or bottom wall whichever closer to their initial balancing positions. This in turn increases the component of F_D to balance out increased F_C, leading to formation of new particle balance point at Position #1. If the flow rate continues to increase, F_C will become dominant and no other forces can balance it laterally, therefore particles will move to outer side and eventually trapped in one of the vortices center (Position #4) due to the strong Dean flow there. Since all of the forces are related to the size of particle, the flow rate for them to shift from Position #1 to #4 is size-dependent, which makes size based separation available.

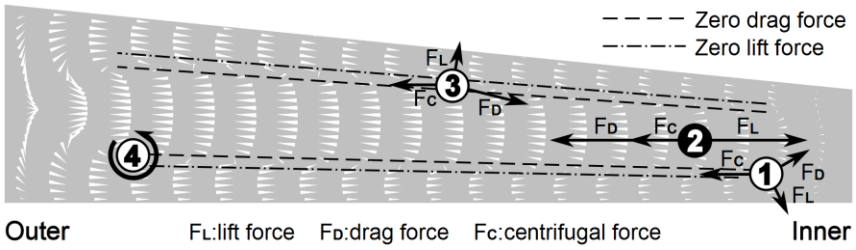

Figure 4: Schematic diagram illustrating the direction of forces on particles at different positions. Black circles indicate locations of unstable balanced point. White circles indicate stable force balanced point at either upper or lower half of channel. White cone indicate the direction and logarithmic magnitude of Dean velocity.

CONCLUSION

We developed a trapezoidal cross-section spiral microfluidic channel for size based particles separation. The experimental result conclusively shows that the new channel is able to achieve high resolution and high throughput cell separations. We successfully separated 16.68μm and 26.9μm particle at 1.33% concentration under 3.4mL/min with over 96% efficiency, which is the highest throughput and efficiency among the microfluidic methods so far. The mechanism of particle focusing was studied by observing the position of forces balanced particle streams, along with the numerical simulation of Dean flow field. The analysis indicates that particles are focusing at location where inertial lift force and Dean drag force are not dominant, and that centrifugal force should be considered for the explanation of particle force balance.

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