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Enhanced blood plasma separation by modulation of inertial lift force

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ABSTRACT

This paper describes enhanced blood plasma separation by modulating the inertial lift force for separation in a contraction–expansion array (CEA) microchannel. By changing a contraction channel length, we observed the force modulation effects for size-based particle separation. In the CEA device, there are two force components that act in opposite direction to separate particles by size. By lengthening the contraction region in the CEA microchannel, we can easily control the lateral migration of desired particles by modulating a single force component (inertial lift force) without affecting the other (Dean drag force). From the experimental results, the inertial force ratio was calculated for prediction of force superiority between inertial lift force and Dean drag force, and applied to determine design parameters of the CEA microdevice for blood plasma separation. Using the force modulation in the microchannel, we successfully demonstrated enhancement of inertial blood plasma separation from human whole blood with a substantially high blood cell rejection ratio and a separation yield of 92.6% and 69.5%, respectively, with a throughput of 5.4×10^{11} cells/min.

1. Introduction

Blood, mainly composed of blood cells and plasma, provides a massive amount of information about a person's health condition [1]. Blood plasma in particular is clinically used to analyze the inflammatory response of a patient and is also used for proteomic studies [2]. Conventionally blood plasma has been separated from the blood cells by bulk bench-top method, which is labor intensive and can have a confounding effect on the sample. Centrifugation of blood cells during the separation process can activate cells [3–5], and for example, affect the concentration of critical factors of analysis such as eosinophil activity markers [4]. Not only the sample should be treated carefully during the separation, sometimes the separation process also needs to be performed quickly within half an hour to 1 h after sampling [4] with proper storage conditions, which calls for a need for a portable device with high throughput that can process samples in a timely fashion. Depending on the analyte of interest, the separation also requires a high yield of plasma due to the low abundance of certain proteins in the blood [6]. Furthermore, separating plasma with high purity is important because blood cells can interfere with optical measurement techniques and alter the separation results [7].

Development of microfluidics systems of plasma separation seems to provide promising solutions to overcome the limitations of conventional separation method. As a consequence, many research groups reported miniaturized on-chip plasma separation systems. One of the earlier methods utilized filters to remove blood cells [8], however, the filter was clogged with accumulated blood cells and resulted in decreased separation efficiency. To avoid using filters, continuous blood plasma separation methods have been demonstrated by utilizing fluidic phenomena such as Fahraeus effect [9] and Zweifach–Fung effect [10], however, the two methods are performed at low flow rates in the order of 10–100 μL/h.

Recent advances in inertial microfluidics allow the application of inertial lift force and Dean flow within a microchannel and various designs are introduced for separation of particles with different sizes at the milliliter scale [11]. Separation of particles or cells utilizing inertial lift force and Dean flow was performed in a straight channel [12,13], spiral shaped channel [14,15], and a channel with a series of arches with alternating curves [16]. Although they utilized the balance of the two forces to demonstrate focusing and separation of various types of cells and particles, including red blood cells (RBCs), white blood cells (WBCs) and circulating tumor cells, their designs have not been applied to blood plasma separation from whole blood.

Previously, we demonstrated inertial blood plasma separation from whole blood by changing the channel aspect ratio in a contraction–expansion array (CEA) microchannel, resulting in a blood cell rejection ratio of 60%, a separation yield of 62.2% and

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a throughput of 1.2 mL/h (~1.0×10^8 cells/min) [17]. Even though the previous study showed the method for obtaining the separation criteria using the force balance between inertial lift force and Dean drag force by changing the channel aspect ratio, the control of particle migration is limited because changing the channel aspect ratio affects both inertial lift force and Dean drag force simultaneously, which are attributed to the low blood cell rejection ratio. In this paper, to be able to modulate a single force component without affecting the other, we investigated force modulation effects by change of the contraction channel length in a CEA microchannel and demonstrated enhanced blood plasma separation. By increasing the length of the contraction channel, modulation of the force balances can be achieved by reinforcing inertial lift force while sustaining fixed Dean drag force, which offers simple engineering criteria to determine the particle migration. The longer contraction channel increases the duration at which blood cells are exposed to inertial lift force, causing them to migrate further away from the side where plasma is, thereby increasing the blood cell rejection ratio. The ability to control a single parameter without affecting the other allows more versatile force modulation, which is an essential feature in proper target cell separation.

2. Design principle

Fig. 1(a) shows a schematic of inertial blood plasma separation in a CEA microchannel. In the contraction channel, inertial lift force and Dean drag force are induced, each having opposite direction to each other. The force balance between inertial lift force and dean drag force determines the lateral positions of cells, whereas the lateral position of plasma fluid is determined by Dean flow. Particles such as RBCs and WBCs are dominantly influenced by inertial lift force, migrating toward sidewall 1 (s1), while fluids such as blood plasma are dominantly influenced by Dean flow, migrating toward sidewall 2 (s2). From this mechanism, the blood plasma can be extracted from whole blood samples. Because the force balance in a CEA microchannel determines the lateral positions of cells and the bifurcation point at which samples are separated, it is necessary to exploit the force balance for proper target cell size-based separation. The bifurcation point can be modulated by changing the contraction length.

The accumulated lateral migration induced by Dean flow is related to the number of contraction region because the dean flow occurs only at the entrance of the contraction region [18–20]. But the accumulated lateral migration due to inertial lift force is related to the length of the contraction region because the inertial lift force on particles is induced throughout the length of the contraction region [21]. In the CEA microchannel, the large particles (red color) are dominantly influenced by inertial lift force and migrate toward sidewall 1 (s1) (Fig. 1(b)). By lengthening the contraction region, the large particles can be exposed to inertial lift forces for longer period of time as they flow through the long contraction region as shown in Fig. 1(c); resulting in farther migration toward s1. However, small particles are dominantly influenced by Dean flow and migrate toward sidewall 2 (s2) with similar lateral positions in both cases due to the fixed magnitude of Dean flow. From this modulation of the force balance with varying contraction region length, the lateral migration of particles can be determined by controlling only one of the force components without simultaneously affecting both inertial lift force and Dean drag force.

3. Experimental

3.1. Design and fabrication

The CEA microchannel was 350 μm wide, with contraction regions of 50 μm wide and 150, 300, 600, and 1200 μm long in each device for investigation of the effect of contraction region length on particle migration. The contraction regions were formed with six rectangular structures in the microchannel (Fig. 1(d)). The number of entrances to the contraction regions, which is related to the effect of Dean flow, was fixed as 6 because the purpose of this study was to investigate the effect of changing the contraction region length. The interval between contraction regions was chosen to be 700 μm to minimize the effect of vortex formation on flow path at high flow rates since the vortex can act as a wall and deviate the particle trajectories. Fig. S1 shows that the effect of vortex on flow path is smaller in 700 μm long expansion region compared to that in 300 and 1100 μm long expansion region, which indicates that the effect of vortex formation on flow path is minimal at this length. The height of the CEA microchannel was with 25 μm. The CEA microchannel was fabricated in poly(dimethylsiloxane) (PDMS) using soft lithography techniques. A mixture of PDMS prepolymer and its curing agent (Sylgard 184; Dow Corning, MI) in the ratio of 9:1 was poured on the SU-8 photoresist molds and cured

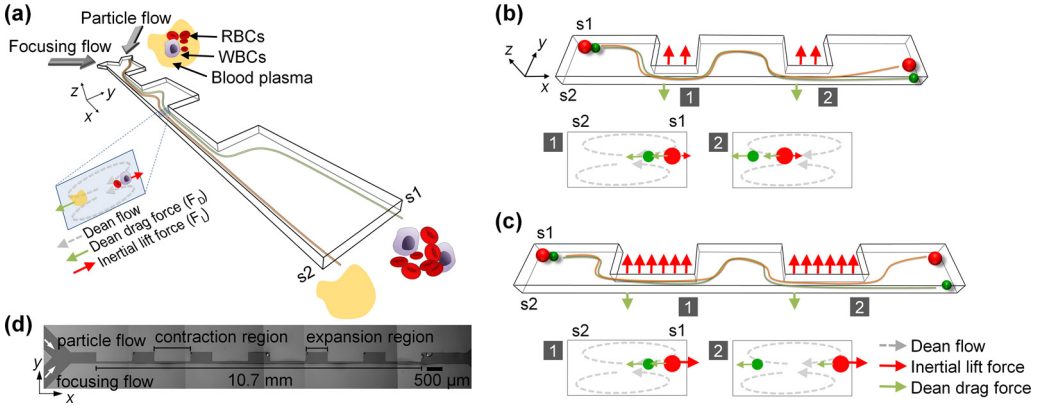

Fig. 1. (a) Schematics of proposed contraction-lengthened CEA microchannel for modulation of inertial migration. Whole blood flows along sidewall 1 (s1) of the channel by a focusing flow and experiences both Dean drag and inertial lift forces, each being induced by Dean flow at the entrance of the contraction region and shear induced lift force along the contraction region. The RBCs and WBCs migrate toward s1 by dominant inertial lift force, while blood plasma entrains in Dean flow toward sidewall 2 (s2) by dominant Dean drag force. (b and c) Modulation of force balance by change of the contraction length. The direction of particle migration is determined by balancing the magnitudes of the two forces: (1) inertial lift force and (2) Dean drag force. The longer the contraction length is, the particles are influenced by inertial lift force for longer period of time. From this mechanism, the large particles migrate farther toward s1 in the CEA microchannel whose contraction length is four times longer for (c) compared with (b). (d) Micrograph of the fabricated CEA microchannel with a contraction length of 1200 μm. The CEA microchannel was 350 μm wide and 25 μm deep with contraction regions 50 μm wide and 1200 μm long. The interval between contraction regions was 700 μm.