Separation of plasma from blood using a dielectrophoresis-assisted microfluidic device: a computational fluid dynamics study

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Abstract
This paper presents a microfluidic device using dielectrophoresis to separate plasma from blood. The device comprises a main channel, five lateral channels, and four microelectrodes. The performance of the system is evaluated by directing the plasma through the lateral channels and blood cells through the main channel. Simulations were performed for three different concentrations of red blood cells. It is found that the separated plasma purity increases with increasing the applied voltage to the microelectrodes. In addition, increasing the flow rate increases the required applied voltage for attaining desired separation. Finally, it is observed that a plasma purity of 100% with the plasma separation of 65% could be obtained at the flow rate of 0.01 mL/min and the applied voltage of 107 V with the applied voltage frequency of 1 MHz.

Keywords: Microfluidics, Dielectrophoresis, Separation, Blood plasma;

Introduction
Human blood is composed of leukocytes or white blood cells (WBCs), erythrocytes or red blood cells (RBCs), platelets, and plasma [1]. Red blood cells, which account for 98% of all blood cells, have a discoid shape and are 7 to 8 µm in size. Plasma is an aqueous medium free of cells that acts as a host to a myriad of analytes containing metabolites, proteins, circulating nucleic acids, and other organisms. Many medical diagnoses require the separation of plasma from blood, where the accuracy of the diagnoses depends on the plasma being totally free of red blood cells [2].

Plasma separation is conducted in several ways, where among them, two conventional methods - centrifugation and filtration - remain the most common ones in the laboratories. While those methods are simple, the employed procedures are laborious and time consuming [2]. Accordingly, in recent years, advances in the separation of plasma have been made through employing microfluidic devices. Microfluidic techniques have many advantages over conventional methods such as short analysis time, being user-friendly, and capability of automation. Employing microfluidic devices results in less analysis cost and miniaturization of the analysis device, making it attractive for portable and low-cost analysis of biological samples.

Microfluidic techniques for separation of plasma are categorised as passive and active. In the passive methods, bioparticles can be sorted by their physical characteristics such as size,
shape, and density using only geometrical characteristics of microchannels, fluid flow, and hydrodynamic forces. Sedimentation is the oldest passive method that has been adapted in microscale systems for collecting plasma [3]. Although undiluted whole blood can be operated in microfluidic sedimentation devices, the separation throughput is relatively low as any increase in the flow rate causes inefficient separation.

Microfiltration is another example of taking the macroscale principle into the microscale world for plasma separation. Such separators have been appeared in two general categories: membrane-based and membrane-free devices. In membrane-based separators, a membrane is sandwiched between microchannels. Membranes have been designed to prevent blood cells from passing through so the plasma can be extracted from the blood [4]. In membrane-free separators, in general, one main channel and few lateral channels are employed with the bioparticles being left from the main channel and the plasma from the lateral channels. However, the major drawback in these methodologies is the problem of clogging and low purity of the separated plasma.

On the other hand, in the active methods, external forces such as acoustic, magnetic, and dielectric forces can be used to sort and separate micro and bioparticles. Among the forces, while dielectrophoretic (DEP) forces are well-established for the manipulation of micro and bioparticles, the forces have been rarely employed for the plasma separation. The dielectrophoretic-based methods allow plasma separation using an electrical force caused by an inhomogeneous electric field [5]. However, the methods require diluted blood samples, direct contact between blood samples and electrodes, and high applied voltages [6]. Accordingly, the blood cells could be damaged, and hemoglobin secreted from the ruptured blood cells could pollute the separated plasma. Also, the applied high voltage may cause bubble formation and the detrimental effect of joule heating.

In this paper, we report a hybrid microfluidic device to separate plasma from blood with high throughput through combining microfiltration-based and DEP-based methods. For this purpose, a microfluidic device consisting of one main channel and five lateral channels is employed with the blood cells being left from the main channel and the plasma from the lateral channels. Also, four microelectrodes, coated with a layer of polydimethylsiloxane (PDMS), are located at the lower surface of the main microchannel to generate non-uniform electric field required in dielectrophoresis-based separation. PDMS prevents direct contact of the sample with electrodes to avoid problems from direct contact. The non-uniform electric field generated by the electrodes imparts negative dielectrophoretic force on the blood cells, preventing the cells entry into the lateral channels.

**Simulation and methods**

Fig. 1 shows the schematic representation of the microfluidic device. In this study, COMSOL Multiphysics version 5.2, which is a finite element-based software, was employed to simulate three dimensionally the microfluidic device. In the simulation of the microfluidic device, the parameters are divided into geometric and operational classes. The geometric parameters are considered constant, and operational ones are varied in the ranges, reported in Table 1.

In our simulations, the laminar flow module is used to solve the fluid flow. The non-slip boundary condition is considered for the channel walls and the pressure at the outlets is set to zero. An electric current module is used to calculate the non-uniform electric field and, finally, in order to detect RBCs, a particle tracing module coupled with DEP and drag forces is used.
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Fig. 1 Schematic representation of the microfluidic device

Table 1. Geometric and operational parameters used for the simulation of the microfluidic device

<table>
<thead>
<tr>
<th>Type</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric (constant)</td>
<td>Main channel width (µm)</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>Lateral channels width (µm)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Depth of the microfluidic device (µm)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Number of lateral channels</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Lateral channel spacing (µm)</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Number of electrodes</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Electrode width (µm)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Electrode length (µm)</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Electrode spacing (µm)</td>
<td>200</td>
</tr>
<tr>
<td>Operational (variable)</td>
<td>Flow rate (mL/min)</td>
<td>0.01, 0.025, 0.05</td>
</tr>
<tr>
<td></td>
<td>Voltage (V)</td>
<td>96-234</td>
</tr>
<tr>
<td></td>
<td>Volumetric percentage of red blood cells in the blood (vol.%)</td>
<td>0.03, 0.06, 0.12</td>
</tr>
</tbody>
</table>

The DEP force arises from the polarization of the cells in the non-uniform electric field. When a neutral or charged particle is polarized in a suspending liquid under the influence of a non-uniform electric field, a charge distribution expands throughout the particle volume and the particle moves towards or away from the maximum field gradient under the influence of the DEP force. The DEP force on a particle is given by:

\[
F_{DEP} = 2\pi \varepsilon_m r_p^3 \Re \left[ f_{CM} \right] \nabla \left( E_{RMS} E_{RMS} \right),
\]

where \( \varepsilon_m \) is the permittivity of the medium, \( r_p \) is the radius of the particle, \( E_{RMS} \) is electric field amplitude. Also, \( \Re \left[ f_{CM} \right] \) is the real part of the Clausius-Mossotti (CM) factor, which determines whether the DEP is positive or negative. The CM factor is given by:

\[
f_{CM} = \frac{\varepsilon_p - \varepsilon_m}{\varepsilon_p + 2\varepsilon_m},
\]

where \( \varepsilon_p \) and \( \varepsilon_m \) are the complex permittivities of the particle and medium, respectively, which depend on the electric conductivities and frequency of the electric field as:

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\varepsilon = \varepsilon - \frac{\sigma}{i\omega},
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\[\text{where} \quad \varepsilon_p \quad \text{and} \quad \varepsilon_m \quad \text{are the complex permittivities of the particle and medium, respectively, which depend on the electric conductivities and frequency of the electric field as:}

\[
\varepsilon = \varepsilon - \frac{\sigma}{i\omega}.
\]
with $i = \sqrt{-1}$ being the imaginary unit, $\varepsilon$ the real permittivity, $\sigma$ the electric conductivity, and $\omega$ the angular frequency of the electric field. In our simulations, the frequency of the electric field is set at 1 MHz. Therefore, according to Fig. 2, the CM factor was negative at the frequency for RBCs, ensuring a negative DEP on the cells.

![Fig. 2 Clausius-Mossotti factor for RBCs.](image)

The drag force can be expressed using the Stokes law:

$$F_{\text{drag}} = 6\pi \eta r p V,$$

where $\eta$ is the viscosity of the medium and $V$ is the velocity of the flow.

**Results and discussion**

In this study, we investigated the effect of three experimentally controllable parameters on plasma purity and separation efficiency from blood. The plasma purity is given by:

$$PP = 1 - \frac{n_{\text{lateral}}}{n_{\text{main}}},$$

where $n_{\text{lateral}}$ is the number of output RBCs from the lateral channels and $n_{\text{main}}$ is the number of inlet RBCs from the main channel. Also, the plasma separation is given by:

$$PS = \frac{V_{\text{plasma}}}{V_{\text{total}}},$$

where $V_{\text{plasma}}$ is the volume of output plasma, and $V_{\text{total}}$ is the volume of injected blood sample.

Our simulations were conducted for 150 s of which 120 s was for achieving steady-state conditions. The data till 120 s were discarded and the results of the last 30 s were gathered for analysis purposes.

Fig. 3 shows the plasma purity as a function of the applied voltage at various concentrations of RBCs and flow rates. According to the results, with increasing the flow rate, the applied voltage increases. In addition, increasing the concentration of the RBCs at a given voltage has a negative effect on the plasma purity. However, the purity of 100% is achieved at the applied
voltages of 107, 170, and 234 V for the flow rates of, respectively, 0.01, 0.025, and 0.05 mL/min.

Fig. 3 Plasma purity as a function of the applied voltage at the flow rate of 0.01 (A), 0.025 (B), and 0.05 mL/min (C).
Fig. 4 shows the plasma separation as a function of flow rate with and without applied voltage. According to the figure, the amount of plasma extracted from the blood decreases with increasing the flow rate. However, with the applied voltage, the separation efficiency is more than that in the absence of the electric field.

**Conclusions**

In this study, we proposed a microfluidic device through combining membrane-free microfiltration and dielectrophoresis bioparticle manipulation for the separation of plasma from blood. The device consists of a main channel, five lateral channels, and four microelectrodes. It was found that the separated plasma purity increases with increasing the applied voltage to the microelectrodes. On the other hand, increasing the flow rate increases the required applied voltage for attaining desired separation. Finally, the proposed microfluidic device must be optimized through considering geometric and operational parameters to obtain the highest plasma separation and purity.

**References**


