MAGNETICALLY-ACTUATED BLOOD FILTER UNIT ATTACHABLE TO BIOCHIPS

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ABSTRACT

A novel blood filter unit for the separation of blood plasma from whole blood by simple magnetic actuation is presented. A non-diluted blood sample is introduced into the filter unit and, only blood plasma is squeezed out by magnetic attraction force, while blood particles are filtered by membranes stacked in the filter unit. The new filter unit is very simple, but yields good filtering performance with nearly perfect filtering efficiency (~99.999%), high plasma recovery (~30%), low blood consumption (<50 μl), and fast operation (~1 minute). Also, the filter unit can be mass-produced for disposable use, and can be attached to any kind of biochips. Because the present filter unit is simple, fast, convenient, low-cost, compatible, and highly efficient, it has commercial potential for various lab-on-a-chips for blood tests.

KEYWORDS

Blood filter, plasma separation, magnetic actuation.

INTRODUCTION

The removal of cellular components is regarded as a requisite pretreatment step for most clinical blood tests for the high-sensitive and reproducible results. Because filteration at macroscale (e.g., centrifuge) is slow and laborious, many research groups have developed microfluidic blood filters utilizing a lot of principles. The blood cells were filtered or displaced by fine structures [1], packed beads [2], obstacles [3], electrical fields [4], acoustic waves [5], light sources [6], gravitational or centrifugal accelerations [7], and various hydrodynamic phenomena [8] (e.g., the plasma skimming effect, Fahraeus effect, pinched flow fractionation effect, Zweifach-Fung effect, dean flow, etc.).

However, these filter devices usually possess some drawbacks (e.g., clogging, complexity in fabrication and operation, slow speed, low plasma recovery, expensive materials, large sample volume, and complex instrumentation) and can be utilized under limited conditions (e.g., dilution ratio, flow rate, etc.). Our goal in this study is to develop a simple and versatile filter overcoming these limitations with the aid of magnetism. Here, we propose an innovative design and filtering principle to achieve the aforementioned requirements.

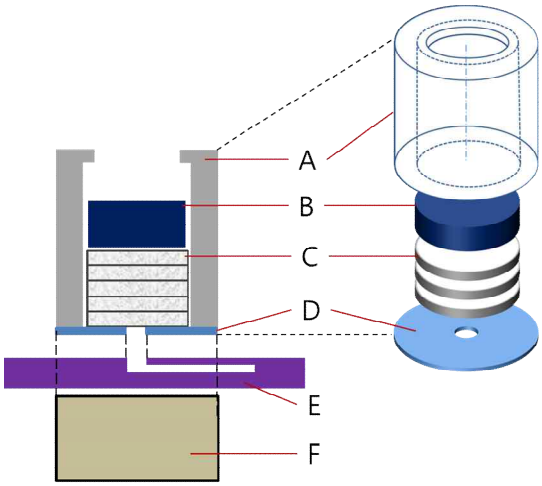


Figure 1. A schematic diagram of the blood filter. A: plastic container; B: permanent magnet; C: filter membrane; D: double-sided tape; E: biochip; F: external control magnet.

EXPERIMENTAL

Schematic diagram of the filter device is shown in Figure 1. For a filter unit, one permanent magnet and a few membranes are stacked in a plastic container. Double-sided tape is attached to the bottom of the unit in order to be attached to premade biochips. The outlet of the filter unit is aligned with the inlet of a biochip to create a path through which plasma from the filter unit flows into a biochip. A movable external control magnet is placed below a biochip in order to attract the permanent magnet in the filter unit and squeeze the layered membranes.

The blood filters of some different size and a microfluidic chip to measure the volume of extracted plasma are fabricated and an experimental setup was prepared to test its performance (Figure 2).

One magnet (diameters of 3, 4, & 5 mm, length of 3 mm, Nd-Fe-B) and a few punched membranes of the same diameter were inserted into a cylindrical container (fabricated by machining an acrylic plate) with a little larger inner

diameter. The double-sided tape was punched to make disk-shaped outlines and an inner hole.

Some parameters for performance tests are defined as: T_w, waiting time between the sample introduction and the application of the external magnet; N_m, number of membranes inside the filter unit; V_{WB}, volume of whole blood; ϕ, diameter of the membranes. For relative comparisons, a reference condition was fixed at T_w = 60 s, N_m = 5, V_{WB} = 50 μl, and ϕ = 4 mm. We measured the volume of extracted plasma, V_p, and calculated the plasma recovery yield, R_p (%, ratio of the extracted plasma volume to total plasma volume in the whole blood sample). The hematocrit of the blood sample was 45.5%.

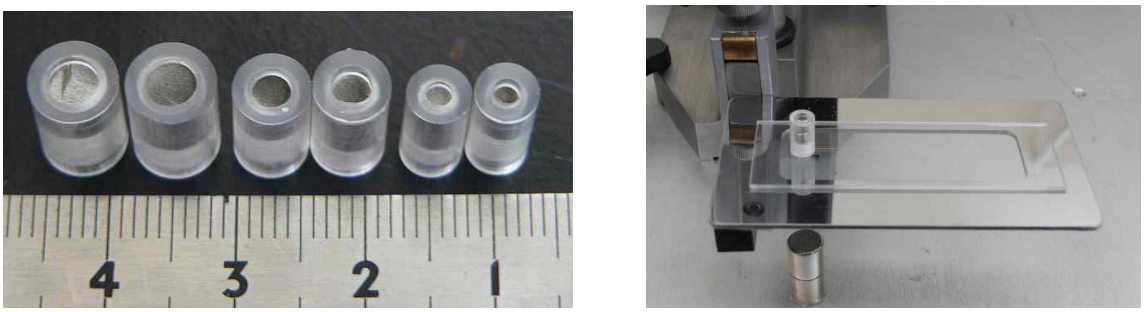


Figure 2. (a) View of the fabricated filter units of different sizes, (b) experimental setup

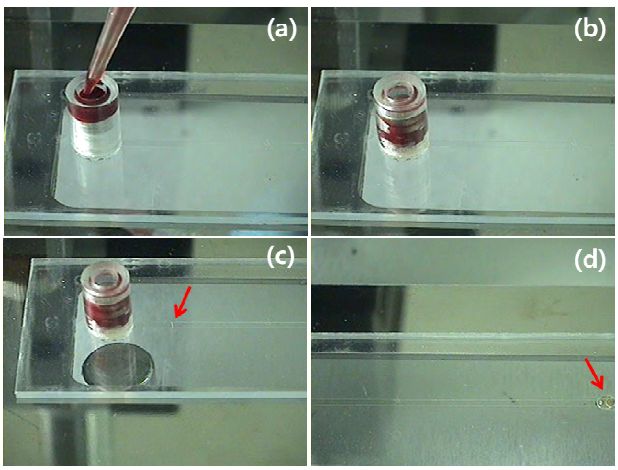


Figure 3. Sequential photos showing the extraction of blood plasma from whole blood. (a) Dropping a blood sample, (b) wetting the membrane, (c) plasma flow into a microchannel by magnetic actuation, (d) collected plasma at the end of the microchannel.

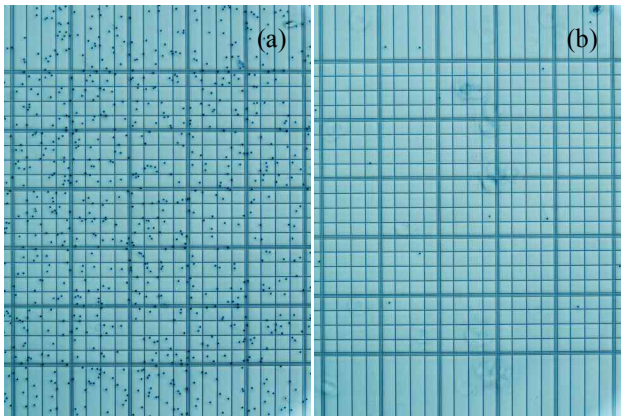


Figure 4. Blood cell count using homocytometer for (a) a thousand-fold diluted blood and (b) plasma obtained from the new filter device

RESULTS AND DUSCUSSION

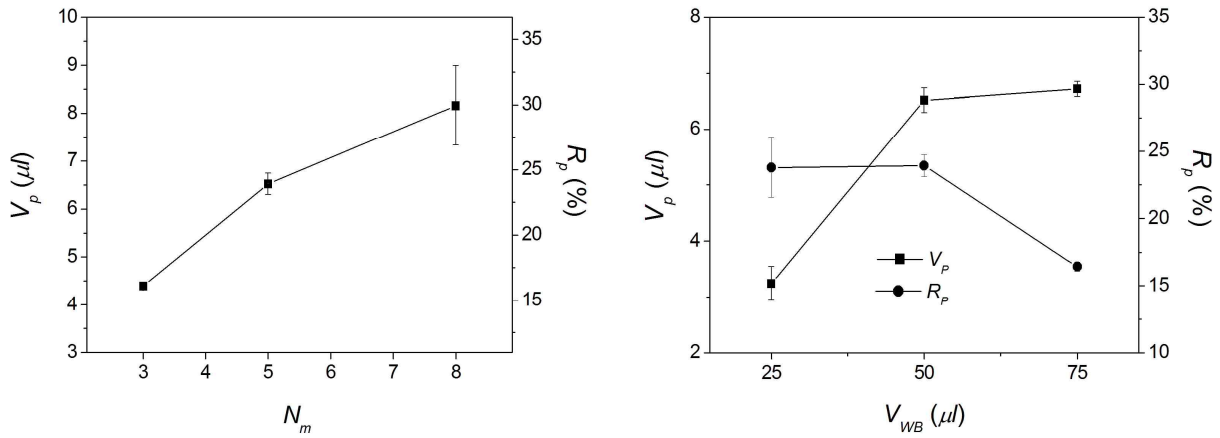
Experimental results on sequential plasma extraction are shown in Figure 3. A drop (50 μl) of whole blood was pipetted into the inlet of the filter unit. We waited 1 minute for the sample to pass through the gap between the magnet and the container and to smear into the membranes. Blood particles including red blood cells were mostly accumulated at the upper side of the membrane, and the plasma component gathered near the bottom. Then, magnetic force was applied to the filter unit by moving the external magnet close to the unit, and the plasma component near the bottom membrane layer started to be squeezed through the outlet of the filter unit and move to the microchannel of the microfluidic test chip. During the squeezing step, the blood particles remained caught by the layered membranes. The separated plasma contains very few blood particles which is counted using a hemocytometer (filtering efficiency ~ 99.999%, see Figure 4).

Figure 5 shows the variation of V_p and R_p with the change of N_m and V_{WB} as the examples of performance test. After a series of performance tests with the filter in the study, the optimized condition was found as: waiting time T_w ~ 1 minute, the number of membrane N_m ~ 8, the volume of the blood sample ~ 50 μl, the diameter of the blood filter ~ 4 mm. For this condition, the filtering performance assumed as: the volume of extracted plasma ~ 8 μl, the plasma recovery yield ~ 30 %.

Compared with other microfluidic filter devices, the present filter has some commercially potentials.

1. The blood sample does not require dilution. Direct use of whole blood is not only helpful for the sensitivity of diagnosis, but it also simplifies the diagnostic process.

2. The filter unit can be applied to various biochips regardless of their materials and geometries. Namely, premade biochips, which are not equipped with blood filters, readily accommodate the blood filtering step with this attachable filter unit.
3. The fabrication and operation of the filter unit are very simple. The unit can be mass produced in a disposable format without difficult fabrication steps and using inexpensive materials. The magnetic operation is readily built into a small instrument.
4. Vertical layering of multiple membranes in the filter unit enhances filtering speed because the total length of the flow path is reduced while the cross-sectional area of the membrane in the flow direction is greatly increased in comparison to the lateral membrane in commercialized strip-type kits.
5. Active squeezing by magnetic actuation greatly reduces sample volume because it minimizes the residual plasma absorbed in the membranes.
6. The filter blood particle removal efficiency is as high as 99.999%, regardless of hematocrit and dilution of the blood sample.



(a) (b)

Figure 5. Blood plasma recovery depending on (a) number of membrane and (b) volume of the blood sample.

CONCLUSION

The filter is very simple, but provides high filtering performance (e.g., fast operation, low blood consumption, nearly perfect filteration, etc.) and some potentials for commercialization (e.g., non-dilution, compatibility to other biochips, simple operation, low cost, etc.). Optimization in the geometrical and operational conditions would further enhance efficiency and volume requirements. Various biomaterials, chemicals, etc., may be applied to the membranes to perform pre-reactions before primary reactions in biochips.

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