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Characterization of a Prototype Compact High Gradient Magnetic Separator Device for Blood Detoxification

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Abstract: A prototype compact magnetic separator device for human blood detoxification was characterized using blood-mimicking fluid (ethylene glycol-water solution) as well as whole blood. Magnetic separation at various applied magnetic fields (0.125, 0.33, and 0.44 T) and various flow rates (3.1–29.5 ml/min) showed that the device could efficiently separate magnetic spheres from blood-mimicking fluid at a moderate applied magnetic field (for example, <0.44 T) and relatively high flow rates (for example, ≤ 29.5 ml/min). The experiments done in flow circulation systems showed that higher flow rates might shorten the sphere recovery time and accelerate the detoxification process. *In vitro* separation from flowing blood showed that it is possible to use the device to efficiently recover spheres in a reasonably short time (≤ 60 min). Moreover, it was also demonstrated that the separator had little effect on the occurrence of hemolysis. All the results revealed that the separator could be a clinically applicable device for efficient separation of magnetic spheres from blood flow for human detoxification purpose.

Keywords: Magnetic separation, magnetic separator, detoxification, nanotechnology, magnetic nanospheres

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INTRODUCTION

The increasing use of medicated and functionalized magnetic spheres in biomedical applications necessitates the development of technologies which selectively and rapidly separate magnetic spheres from the human blood stream (1–12).

A portable magnetic separator device is being proposed for *ex-vivo* magnetic separation (12). It utilizes a dual-lumen needle for arterial or venous access through the skin to provide extracorporeal blood flow through a short segment of a catheter tube. The blood leaving the body flows through this dual-lumen needle, the catheter tube, and into an array of small tubes with ferromagnetic wires placed between each of them. The entire array of tubes and wires is immersed in an externally applied magnetic field. The wires are magnetized and strong magnetic fields and high field gradients are generated to efficiently capture flowing magnetic spheres from the fluid into the tubes. The magnetically filtered blood then flows out of this array through another section of the catheter tube, then the dual-lumen needle, and finally back into the body.

This magnetic separation approach is based on combining two established technologies. The first technology is associated with the high gradient magnetic separation (HGMS) technique (10,13–16), and the second one is associated with the extracorporeal blood circulation technique which is commonly used in hemodialysis (17–19).

In the previous studies (20–22), we investigated the separator design with the aid of 2D and 3D mathematical models as well as *in vitro* flow experiments and selected an optimal configuration in which the wires and the tubes are alternating to each other along both perpendicular and horizontal directions (Fig. 1). In this paper, a prototype compact magnetic separator device is constructed based on this design (Figs. 2 and 3) and

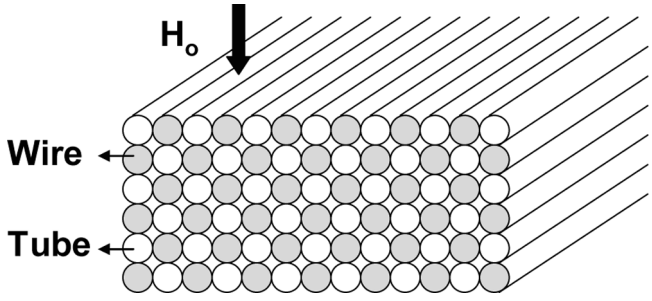

Figure 1. The portable magnetic separator design configuration used in the experiments.

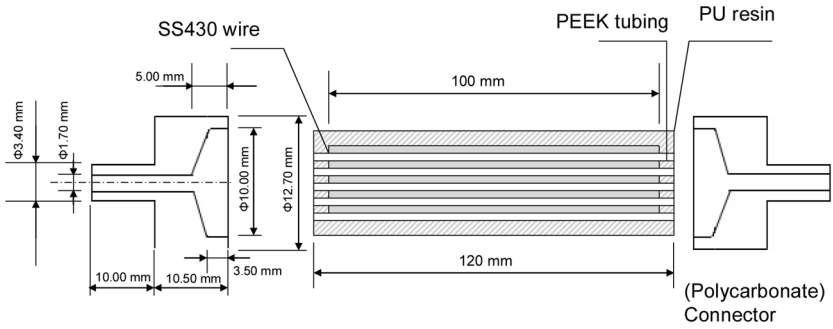

Figure 2. Schematic diagram of the dimensions of the separator device.

a series of *in vitro* flow experiments are carried out to characterize the device.

MATERIALS AND METHODS

Materials

1.7 μm Micromer-M acrylate spheres (12.45% weight/weight magnetite content and 1.05 g/ml in density, Product # 08-06-203) were purchased from Micromod Partikeltechnologie GmbH (Rostock, Germany) (22). The spheres were irradiated to form radioactive ^{59}Fe and a NaI scintillator detector (COBRA^{TM}II Auto-GAMMA®, Packard Instrument Company, Meriden, CT, USA) was used to detect gamma radioactivity to indicate sphere mass concentration of the samples from the experiments.

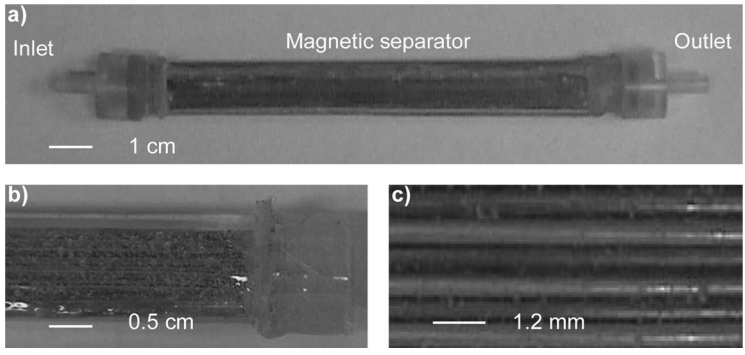

Figure 3. The compact magnetic separator device.

Straight stainless steel 430 (SS430) wires (0.25 mm in radius) were purchased from California Fine Wire Company (Grover Beach, CA, USA). Fine bore polyetheretherketone (PEEK) tube (0.25 mm inner radius and 0.30 mm outer radius) was from RAUMEDIC Inc. (Leesburg, VA, USA). Ethylene glycol (99 + %, spectraphotometric) was purchased from Sigma (St. Louis, MO, USA). NdFeB magnets ($4 \times 4 \times 1.25$ inches) were from Magnet Sales & Manufacturing Company, Inc. (Culver City, CA, USA). The human whole blood was donated by a healthy volunteer according to university guidelines. The blood was drawn into EDTA containing blood collection tubes.

Portable Magnetic Separator

The specific dimensions of the device are shown in Fig. 2. The device consisted of 50 straight SS430 wires (10 cm in length) and 50 PEEK fine bore tubes. The wires and tubes were in the configuration as shown in Fig. 1.

The whole tube-wire matrix was built layer by layer. Each layer contained 5 tubes and 5 wires alternative to each other. The wires and tubes were fixed by epoxy to stay in position. The inlet and outlet connectors were made of polycarbonate (Fig. 3). After the construction, the device was left at room temperature overnight to harden the adhesive. Then the device was coated with heparin by infusing heparin solution (5.0 ml) through the device at a speed of 2.0 ml/h.

Flow System

The experimental set-up (Fig. 4) consisted of a reservoir (50 ml), a 7521-55 *Masterflex*® peristaltic pump (Cole-Parmer Instrument Company, USA), a compact magnetic separator device described above, a receiving

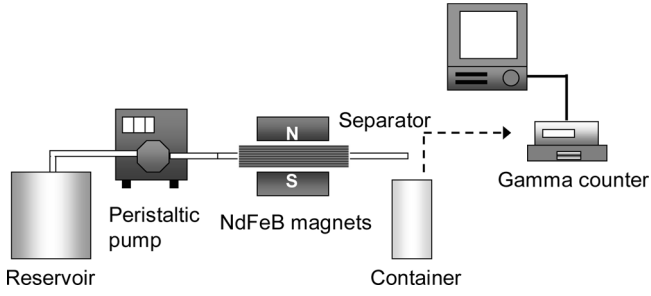

Figure 4. The experimental set-up for *in vitro* magnetic separation.

container and connecting tubes. The concentration of the samples was indicated by gamma activity (23). In this flow-through system, the experiments were carried out to investigate the effects of flow rate and applied magnetic field on the performance of the device. For the experiments carried out in the flow circulation system, the outlet tube from the device was connected back to the reservoir and there was no container in the system, and other components were the same as those in Fig. 4. The effect of flow rates was studied in the flow circulation system using blood-mimicking fluid as well as whole blood. In addition, the effect of the device on the hemolysis was also preliminarily investigated.

Capture Efficiency Evaluation

The capture efficiency (CE) was calculated using:

$$CE = \frac{C_{\text{before}} - C_{\text{after}}}{C_{\text{before}}} \times 100 = \frac{CPM_{\text{before}} - CPM_{\text{after}}}{CPM_{\text{before}} - CPM_{\text{control}}} \times 100 \qquad (1)$$

where C_{before} and C_{after} were the concentrations of the samples before and after magnetic separation, respectively. CPM_{before} and CPM_{after} were radioactivity in counts per minute (CPM) of the samples before and after separation, respectively. CPM_{control} was the CPM of the control sample, which was the pure fluid solution without magnetic spheres. The experiments were run in triplicate for each condition and the data point corresponds to the average value.

Magnetic Separation from Blood-Mimicking Fluids

The fluid used in the experiments was 44% (v/v) ethylene glycol–water solution (viscosity of 3.5 cp at 20°C) to simulate human blood at physiological conditions (for example, 37°C). The concentration of the spheres was 0.04 mg/ml ($\sim 1.5 \times 10^7$ spheres/ml suspension). The change of sphere concentration in the sample was indicated by the gamma radioactivity detection and the CE was calculated from Eq. (1).

To study the effect of the flow rate and applied magnetic field, the variables were varied between 3.1–29.5 ml/min and 0.125–0.44 Tesla, respectively. The experimental set-up was shown in Fig. 4. 25 ml fluid was used for each experiment.

The flow rate was varied between 3.1–38.2 ml/min in each experiment to study the effect of flow rate on the recovery of the magnetic spheres in a flow circulation system with 200 ml fluid. The applied

magnetic field was 0.44 T. The experimental set-up was similar to that in Fig. 4 except that the outlet tube from the device was connected back to the reservoir and there was no container in the system. The fluid in the reservoir was sampled at 10, 30, and 60 min.

All the experiments were carried out at 20°C. The experiments were run three times for each condition and the data point is the average value.

Pressure Drop Measurement

The pressure drops in the device at various flow rates (3.1–38.2 ml/min) were measured by a PowerLab data acquisition system from ADInstruments, Inc. (Colorado Springs, USA) as described previously (23). The fluid used in the experiments was 44% (v/v) ethylene glycol–water solutions (viscosity of 3.5 cp at 20°C). The experiments were run three times for each condition and the data point corresponds to the average value.

Magnetic Separation from Whole Blood

A "rat" model was simulated with 25 ml blood circulated at a flow rate of 3.1 ml/min. The dose of the magnetic spheres was 5 mg. The fluid in the reservoir was sampled at 10, 30, and 60 min. A "rabbit" model was simulated with 200 ml blood circulated at a flow rate of 21.1 ml/min and the corresponding dose was 10 mg. The fluid in the reservoir was also sampled at 10, 30, and 60 min. The external magnetic field was 0.44 T. The experiments were run three times for each condition and the data point is the average value.

In vitro Hemolysis during Extracorporeal Blood Circulation

Hemolysis can be determined from the concentration of hemoglobin in the plasma, which can be easily measured using a Spectronic GENESYS spectrophotometer (Thermo Electron Corporation). The blood sample was centrifuged at 1600 × g for 10 min to separate the plasma and red cells, after which 0.2 ml plasma was diluted in 1.0 ml deionized water and the solution was placed in a quartz vial and transmission was measured at 540 nm. The hemolysis ratio (HR) was calculated by (18)

$$HR = \frac{absorbance\ of\ plasma}{absorbance\ at\ complete\ hemolysis\ reference} \times 100\% \qquad (2)$$

The sample at complete hemolysis reference was prepared by shearing a whole blood sample under high speed (60 ml/min) for 4 hours to break up the red blood cells, and the plasma was processed and measured as described above resulting in a reference sample of 100% hemolysis. To eliminate the effect of the pump and the tubes, we first measured hemolysis with the pump and the tubes only in the system, and then the whole system including the device with the connectors. After each experiment, the tubes, the connectors, and the device were rinsed with saline to clean off residual blood and spheres. Then, the device was recoated with heparin as described. During the experiments, the flow rate was maintained at 21.1 ml/min. 25 ml blood was used in each run. The temperature was at 37°C. The duration of each experiment was 2 hours. 1.5 ml blood was sampled from the reservoir at each 30 min and the HR was evaluated using the method described above. Every data point was averaged from three samples. The experiments were run two times.

RESULTS AND DISCUSSION

The device has been designed for future *ex-vivo* biomedical applications, e.g., efficient separation of magnetic nano-/micro-spheres from human blood flow. The task requires not only high capture efficiency but also fast separation. Therefore, a systemic *in vitro* characterization of the device is necessary before *ex-vivo* implementation of the device for blood detoxification.

Magnetic Separation

Fig. 5 shows the effect of applied magnetic field strength ($\mu_o H_o$) at various flow rates. Apparently, larger $\mu_o H_o$ improves CE. When $\mu_o H_o$ increased from 0.125 T to 0.33 T, which was adjusted by changing the distance between the two magnets, the CE increased from 72% to 88% at 31 ml/min. However, no less than 90% CE was still available for $\mu_o H_o = 0.125$ T when the flow rate was less than 5 ml/min. Hence, for the separation of magnetic spheres from small animals such as rats, a relatively small applied magnetic field, for example, 0.125 T, would be enough to fulfill the task due to the small blood flow rate and blood volume available in these animals. Another interesting observation is that in spite of the substantial increase of $\mu_o H_o$, the CE was not improved much when $\mu_o H_o$ increased from 0.33 T to 0.44 T, being 0.2% at 3 ml/min and 1.2% at 31 ml/min. This can be attributed to the superparamagnetic property of the magnetic spheres and ferromagnetic property of the

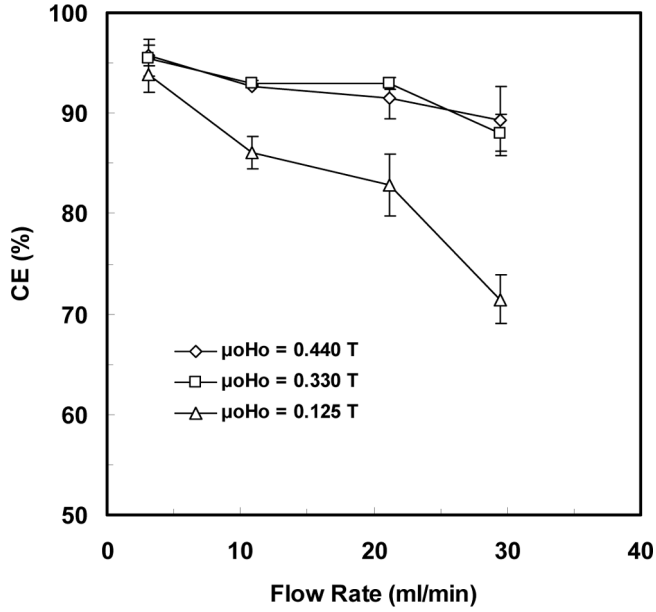

Figure 5. The effect of applied magnetic field ($\mu_o H_o$) on CE, where μ_o is magnetic permeability of vacuum and is equal to $4\pi \times 10^{-7}$.

wires. The magnetic force (F_m) upon a magnetic sphere could be expressed as

$$F_m = \frac{1}{2}\mu_o \omega_{fm,p} V_p \frac{M_{fm}}{H} \nabla(H \cdot H) \tag{3}$$

where μ_o is the magnetic permeability of vacuum, V_p is the volume of the magnetic sphere, and $\omega_{fm,p}$ is the volume fraction of the ferromagnetic material inside the sphere with magnetization M_{fm}. H is the magnetic field at the position of sphere, which is produced by the superposition between the external magnetic field and the one induced by the magnetized wires. When both the wires and spheres are magnetically saturated, further increase in the applied magnetic field will not be able to contribute much in magnetic force. Therefore, in future blood detoxification processes, a moderate applied magnetic field would be enough, which would reduce the cost and improve the safety of the device. It is of importance to see that even at a relatively high flow rate (29.5 ml/min) the device could still attain a high capture efficiency (>90%). The results

from this compact device could be extrapolated for designing a portable device for future human use. Assuming that the blood flow rate in one of the big arteries in human arm is 60 ml/min, then 100 pieces of fine bore PEEK tubes would have to be used in the device in order to get a CE > 90%. Based on the experimental results in Fig. 5 and the human physiological characteristics, the number of tubes in the device could be up to several hundred depending on the specific separation task and mode, i.e., with or without blood pump, which will be stated later. An increase to several hundred tubes would be acceptable considering that the number of fibers in clinical dialyzers is normally around 10,000 (24,25).

We also carried out the experiments on small animal scales in a flow circulation system. The volume used corresponded to the blood volume in normal rabbits. However, we chose a relatively wide range of flow rates in order to determine the effect of flow rate on the separation in a circulation. Of note, in an *ex-vivo* application, it is still feasible to change the flow rate in the device by a mini blood pump, which is a routine technique in current clinical hemodialysis procedure. Fig. 6 shows the recovery of magnetic spheres at various flow rates. The recovery is indicated from the relative sphere concentration, i.e., C/C_o, in the

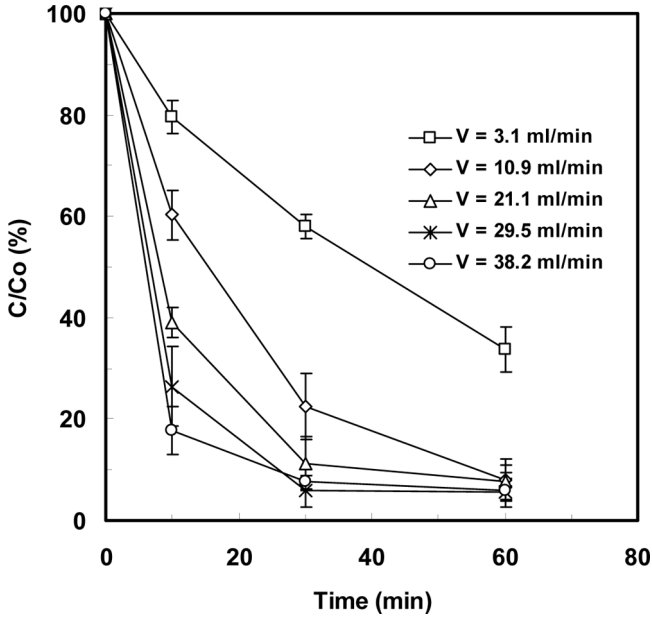

Figure 6. The effect of flow rate on recovery.

container. C_o is the initial concentration. The lower C/C_o is, the higher the recovery will be. It is of importance and of interest that a higher flow rate can lead to faster recovery of the spheres. This can be attributed to the smaller turn-over period, i.e., more turn-over times, available for higher flow rate in a circulation system with a predefined fluid volume. Because faster sphere recovery indicates more rapid toxin-removal and blood detoxification, the flow rate in future devices should be determined based on high one-pass capture efficiency as well as fast recovery of total spheres in the system. However, a very high blood flow in the device might also cause some physiological problems such as hemolysis. Based on the total blood volume in human body (4–6 liters for adults) and the current experimental results, up to 100 ml/min blood flow rate in the device would be feasible and reasonable in order to attain a fast and efficient toxin-removal in human blood detoxification practice.

Fig. 7 shows magnetic separation of spheres from "rat" and "rabbit" models. The blood volume and blood flow rate were specifically chosen to simulate the circulatory system in normal rats and rabbits. Regardless of the difference in the blood flow rate and the blood volume for the two models, the results show similar recoveries. This is probably due to the similar turn-over time for the two models (8.1 min and 9.5 min for

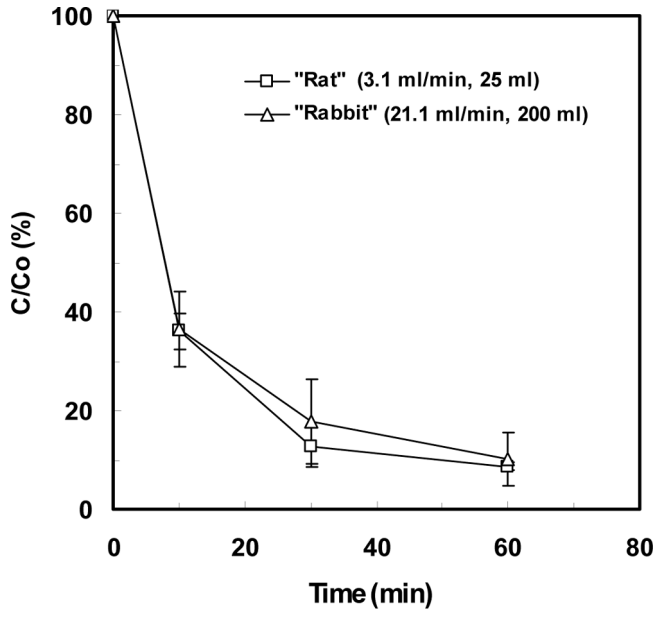

Figure 7. Magnetic separation from blood.

the "rat" and "rabbit" models, respectively). And we can see the sphere concentration in the blood could be reduced to less than 10% of the original concentration in 60 min for the two models, at which 7 passes and 6 passes were used for the "rat" and "rabbit" models, respectively. A lower flow rate might give the system a higher one-pass CE. However, the advantage of the lower flow rate was usually compromised by the higher viscosity of the fluid due to the non-Newtonian behavior of the blood (23) and longer turn-over time as indicated from Fig. 6.

Pressure Drop

Pressure drop is an important technical parameter for a medical device for *ex-vivo* applications. Fig. 8 shows the pressure drops of the device at various flow rates. The fluid used here was 3.5 cp (at 20°C) ethylene glycol solution. When the flow rate increases from 3.1 ml/min to 38.2 ml/min, the pressure drop increases from 7 mmHg to 112 mmHg. It has been noted that the device in the current study was designed for separation on small animal scales, for example, rats or rabbits, which usually have blood flow rates of no greater than 20 ml/min in large arteries. Moreover, according to magnetic separation results in the

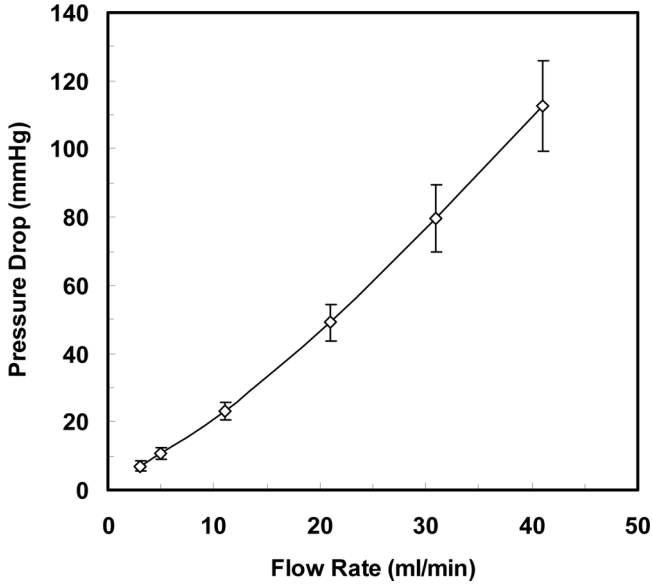

Figure 8. Pressure drop of the device at various flow rates.

previous section, in order to get a one-pass CE > 90%, the flow rate should not be larger than 20 ml/min (this value also depends on magnetic sphere properties such as size and magnetization), which corresponds to about 45 mmHg in pressure drop in this device according to Fig. 8. The device for human detoxification application would be scaled up to accommodate high blood flow rate and to lower the pressure drop.

Basically, there are three options for this magnetic separator device inlet-outlet access to the vessels in the arm: vein-to-vein, artery-to-artery, and artery-to-vein. In vein-to-vein and artery-to-artery configurations, a relatively low blood pressure drop might not be able to push blood through the device at a relatively high flow rate. Therefore, artery-to-vein becomes a better choice. If the inlet is connected to the artery and the outlet is to the vein, which is the same as in most current clinical dialysis process, the big pressure difference between the arterial system and venous system would drive blood flow through the device without the aid of an external blood pump. In this case, the flow rate could be adjusted by a valve on the inlet catheter to control the blood flow rate through the device. However, from a clinical point of view, vein-to-vein may be a better option because of easier access. Then a mini blood pump could be used to achieve proper blood flow rates.

Hemolysis

In traditional dialysis, hemolysis may occur due to flow shearing, pump squeezing, temperature, transmembrane pressure, and dialysate concentration, etc. However, because of the specific structure and application of our magnetic separator device, the transmembrane pressure and the concentration of dialysate would not be the contributing factors. It has been shown that the hemolysis in dialysis is mainly caused by blood flow shearing in the device and pump squeezing (18). The hemolysis caused by the device itself is the focus of this study. To investigate the effect of our compact magnetic separator device on hemolysis, we measured the concentration of hemoglobin in the plasma and converted it to hemolysis ratio using Eq. (2). The maximum shear rate in the device during the experiments was about 1000 s^{-1} when flow rate was 20 ml/min.

Generally, the HR increases with circulation time (Fig. 9). However, even after 2 hours of circulation at 21.1 ml/min, the HR was still no more than 3.5%. Considering that the relative small ratio of blood volume to flow rate in the experiments, the HR due to the device would be lower in an actual blood detoxification application process. Therefore, these results indicate that the device is suitable for *ex-vivo* applications.

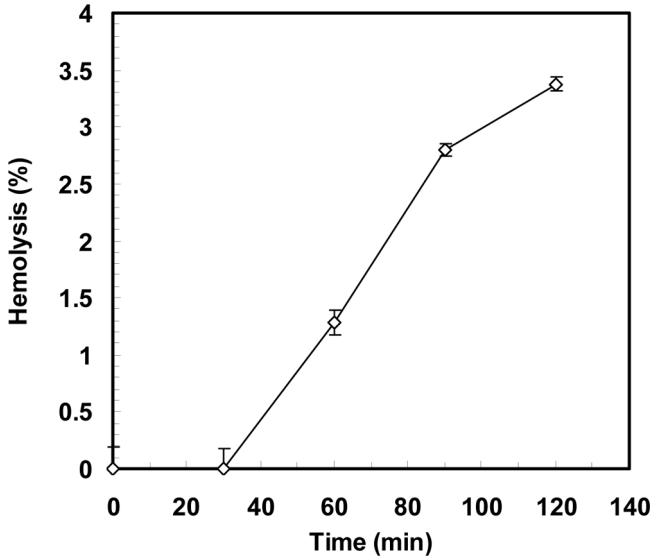

Figure 9. The effect of the magnetic separator device on hemolysis (%). The flow rate was 21.1 ml/min.

CONCLUSION

The prototype compact magnetic separator device was characterized via a series of *in vitro* experiments using blood-mimicking fluid (44% ethylene glycol solution) as well as whole blood.

Magnetic separation at various applied magnetic field (0.125, 0.33 and 0.44 T) and various flow rates (3.1–29.5 ml/min) showed that the device could efficiently separate magnetic spheres from blood-mimicking fluid while at a moderately applied magnetic field ($<$0.44 T) and relatively high flow rates ($\leq$29.5 ml/min). Around 90% capture efficiency was available at $\mu_o H_o = 0.33$ T and 29.5 ml/min. Compared with $\mu_o H_o =$ 0.33 T, an applied magnetic field as high as 0.44 T did not give significantly greater CE, which indicated that a moderate applied magnetic field (0.33 T) would be enough for the system to get a desired CE ($\geq$90%).

Flow circulation experiments showed that higher flow rates might shorten sphere recovery time and accelerate the detoxification process despite that a lower flow rate provided a higher one-pass CE. The faster and more efficient recovery at a higher flow rate could be due to the shorter turn-over in the circulation. *In vivo* experiments using whole blood in flow circulation systems showed that it is possible to use the

device to efficiently recover magnetic spheres on small animal scales in a reasonably short time ($\leq$60 min). Pressure drop measurements for the device showed that when the pressure drop ranged from 7–112 mmHg then the flow rate in the device was from 3–38.2 ml/min. All results revealed that the separator could be a clinically applicable device for efficiently separating magnetic spheres from blood flow for human detoxification purpose.

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