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Journal:	*Lab on a Chip*
Manuscript ID	LC-ART-09-2018-000939
Article Type:	Paper
Date Submitted by the Author:	05-Sep-2018
Complete List of Authors:	Vemulapati, Sasank ; Cornell University, Erickson, David; Cornell University,

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ARTICLE

H.E.R.M.E.S: Rapid Blood-Plasma Separation at the Point-of-Need

Sasank Vemulapati,*[a] and David Erickson

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

The global healthcare landscape is experiencing increasing demand for CLIA-waived testing facilities that offer diagnostic capabilities at lower costs and greater convenience than traditional laboratory testing. While several new diagnostic tools have emerged to fulfill testing requirements in these environments, centrifuges have been stymied from transitioning to the point-of-need as the US Food and Drug Administration (FDA) classifies them as mostly unsuitable for use in CLIA-waived environments. Limitations in sample processing capabilities adversely affects the ability for CLIA-waived testing environments to offer a broad testing portfolio and present-day diagnostics are bottlenecked by the requirement for centrifugation. Here we present the High Efficiency Rapid Magnetic Erythrocyte Separator (H.E.R.M.E.S), a rapid low-cost technology that can perform the separation of red blood cells from plasma at a fraction of the time and cost of that of a centrifuge. We demonstrate that H.E.R.M.E.S is able to obtain highly-pure plasma (greater than 99.9% purity) at less than 2 minutes per test. Further, we detail that it is an easy-to-use method capable of being incorporated with present-day diagnostic technologies and prove that it is superior to existing alternatives to centrifugation by validation with a ferritin lateral flow test. H.E.R.M.E.S is a suitable alternative for centrifugation in point-of-need settings and aims to facilitate the decentralization of commercial blood testing

Introduction

The US blood testing market is estimated at $20 billion and is expected to increase to $30 billion by 2030(1). This predicted growth stems from an increasing demand for CLIA-waived testing environments, such as Urgent Care and Minute Clinics, that offer diagnostic capabilities at lower costs and greater convenience than conventional laboratory testing. CLIA-waived clinics embody a shift in the healthcare landscape towards decentralization and higher accessibility of medical testing. The separation of unwanted cellular material is critical for the accuracy and reliability of many molecular diagnostics tools(2), for example many blood tests require that plasma is separated from red blood cells prior to analysis. In commercial blood testing laboratories, centrifuges are almost exclusively employed to perform separation and is a key first step to facilitate accurate quantitative diagnostics(3). However, the US Food and Drug Administration (FDA) classifies centrifuges as 'moderately' complex devices that are unsuitable for use in CLIA-waived environments(4). This constraint has bottlenecked the translational ability of diagnostic technologies as centrifuges are unable to adapt for use at the point-of-need and are becoming increasingly obsolete in a landscape that is seeking the further decentralization of testing services.

Passive filtration membranes are a solution to perform cell separation at the point-of-need and are often used with lateral flow assays(5). Enabled by capillary action, the membranes operate on the principle of selectively preventing particles of a certain size from flowing through them. While inexpensive and easy to manufacture, the performance of these membranes is marred by inconsistencies in separation caused by clogged pores. Inconsistencies manifest themselves as variability in amount of plasma that is obtained during each run which deters the performance of quantitative lateral flow tests. Immunochemistry is sensitive to a variation in amount of sample that is used for analysis(6,7). Additionally, the recovery rates of these methods is low(8) (less than 30% of available plasma) which presents a barrier for analysis of analytes at low concentrations and sizes(9).

Several microfluidic approaches have been demonstrated in literature that achieve high levels of separation. These methods can be broadly classified into "active" and "passive" techniques(10). Active techniques employ an external field (acoustic, electric or magnetic) that is used to align or immobilize the blood cells so as to enable the plasma to be separated in a continuous flow format. Passive methods typically separate the cells using hydrodynamic effects or separating pillars using cleverly designed and intricate microfluidic fabrication architecture(11–13). While these techniques have been excellent demonstrative proof-of-concepts, they lack the ability to be commercialized as microfluidic fabrication is a highly involved and expensive process that lacks scalability(14). Further, in the case of active methods, the complex designs are often too cost-ineffective to integrate into existing microfluidic methods rendering them

[a] Sibley School of Mechanical and Aerospace Engineering, Cornell University, Ithaca, NY 14850

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

impractical for use at the point-of-need(9). To address the high cost and lack of accessibility, many researchers have used common household items and toys like salad spinners and egg beaters to achieve plasma separation(15–17). These designs were cleverly engineered to simulate centrifugation but are not robust enough to operate in point-of-need clinical settings. There is a need for low-cost technologies that can offer highly efficient blood-plasma separation at the point-of-need with high reliability and efficiency. A 'simple' method would further enable present day diagnostics to transition for use at the point-of-need(18–21) and enable the decentralization of blood testing services.

In this paper we detail the design and principle of the High Efficiency Rapid Magnetic Erythrocyte Separator (dubbed H.E.R.M.E.S), a portable low-cost system that enables the separation and extraction of red blood cells from plasma within 2 minutes. H.E.R.M.E.S uses functionalized magnetic beads to capture and separate red blood cells and achieves near perfect separation, rivaling the efficiency of that of a commercial centrifuge while using inexpensive raw materials. H.E.R.M.E.S employs a standalone protocol that does not require the use of any specialized lab equipment such as pipettes. We demonstrate the efficacy of H.E.R.M.E.S with the help of human samples, and further prove that H.E.R.M.E.S improves the performance of existing lateral flow assays in comparison to commercially available filtration membranes.

H.E.R.M.E.S Device Design Landscape

H.E.R.M.E.S has been designed with a specific intention of being easy-to-use. The process involves three main phases: capture, separation and extraction. In order to obtain separated plasma, the user need only follow three steps (as outlined in Figure 1a), i) collect the sample (typically with a finger-stick) and load the sample in a test tube precoated with functionalized magnetic beads, ii) place sample in H.E.R.M.E.S and wait for 2 minutes, iii) remove sample and extract plasma using a capillary tube. Once the sample has been extracted, the sample can be used for further analysis or stored for future use.

The portable benchtop device itself consists simple onboard electronics to enable automation (Figure 1d). H.E.R.M.E.S employs a small linear solenoid that actuates a magnetic field in a specific direction with respect to the sample to create a mixing effect. This ensures that the beads are able to capture the erythrocytes in the sample. The device occupies a small footprint and can be powered by any standard electrical outlet. Once the device is plugged in, the actuation starts automatically and proceeds for 90 seconds. After 90 seconds, the solenoid turns off and the magnetic beads are concentrated by the magnet on one side of the sample holder. The user then employs a small capillary tube to uptake the separated plasma. While the current iteration requires the use of an outlet, it can be easily re-engineered to include a portable battery pack instead. H.E.R.M.E.S was specifically designed to enable sample processing in point-of-need settings and was designed for semi-autonomous operation to minimize the need for manual intervention by the user.

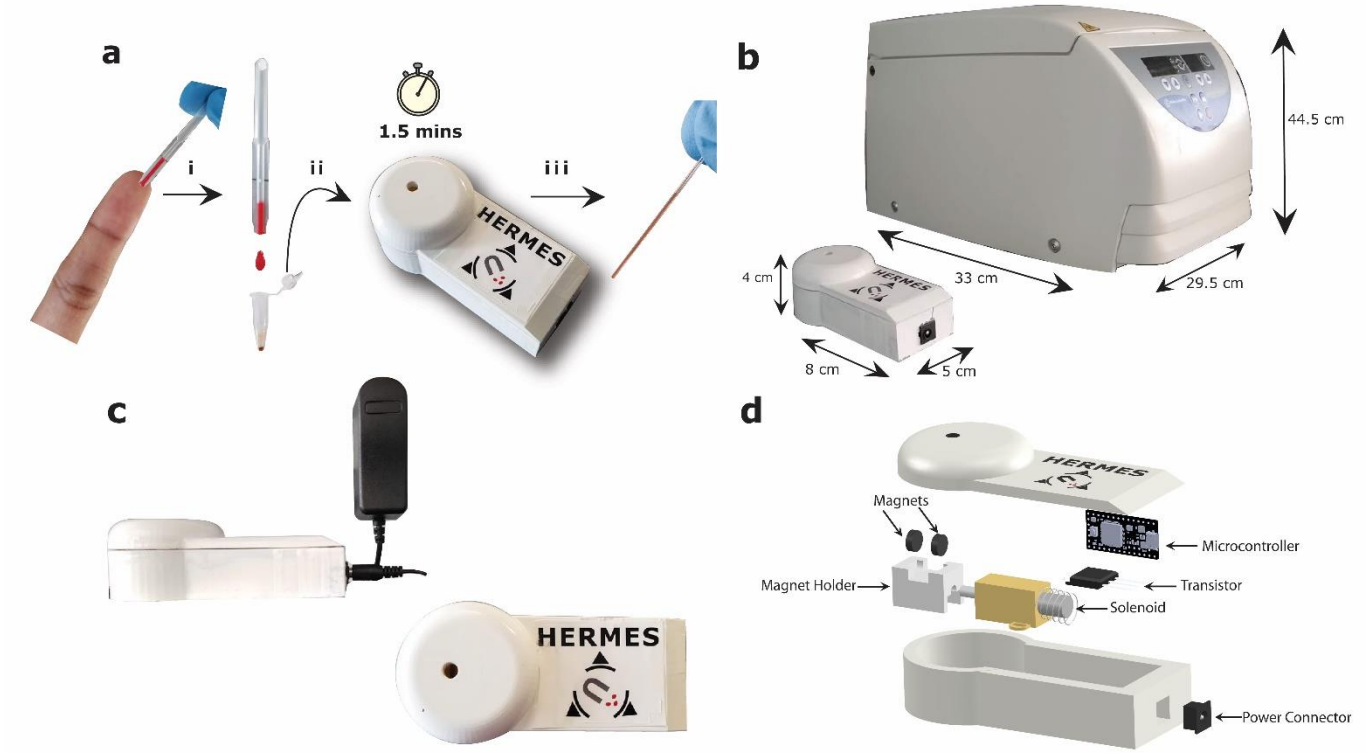

Figure 1: a) Using H.E.R.M.E.S involves 3 simple steps i) collect and load the sample in a test tube precoated with functionalized magnetic beads, ii) place sample in H.E.R.M.E.S and wait for 90 seconds, iii) remove sample and extract plasma using a capillary tube. b) Size comparison of H.E.R.M.E.S against a standard laboratory centrifuge (Fisherbrand accuSpin Micro 17) c) Side and top profile of the portable benchtop device respectively and d) exploded view of H.E.R.M.E.S showing its internal components

Magnetic bead capture of erythrocytes

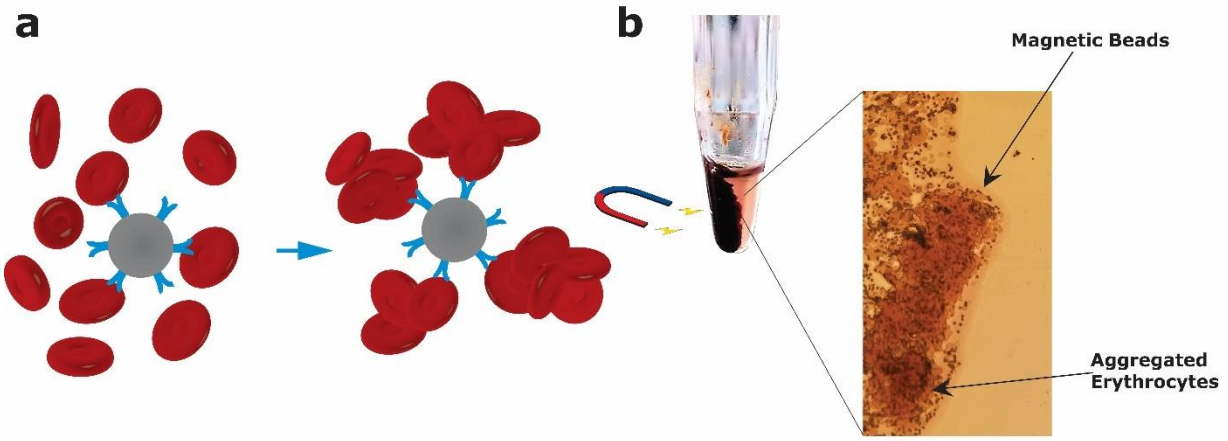

Figure 2: a) Effect of aggregation of blood cells prior to capture and b) Separation of plasma from captured red blood cells with application of a magnetic field *as seen under a microscope*

Magnetic bead based capture has been adopted several biological applications such as DNA extraction, peptidome assessment and immunocapture(22–24). The technique is particularly useful for capturing a small amount of analyte as the beads can be concentrated to yield a higher limit of detection(25). H.E.R.M.E.S tackles the opposite problem: a single microliter of human blood can contain up to 6 million blood cells. This resulted in a significant challenge as it was necessary to capture all the erythrocytes in the sample without the need for dilution. At first glance, it would appear a simple assessment of the binding capacity of the magnetic beads would be sufficient in order determine the minimum number of beads required to capture all the blood cells in the sample. A "brute force" approach as such would be appropriate for separation but would suffer from a lack of scalability. Further, this approach would have a fragile dependence on the sample size with a cost-scaling directly proportional to the number of cells that would need to be captured. In order to maintain a cost-effective scaling principle, H.E.R.M.E.S uses an aggregation agent that groups red blood cells together during the capture phase, thereby reducing the effective number of cells that need to be captured (See Figure 2). By aggregating the cells prior to the capture, we are able to demonstrate an approximate 2000-fold increase in binding capacity of the beads using this aggregation agent. H.E.R.M.E.S is unique in comparison to previous works in literature that employ aggregation enhanced capture as it is performed in an easily accessible format that does not require specialized filtration paper or microfluidic setup(26,27). Our estimations reveal that on average, one bead is able to capture up to 100 cells due to the aggregation effect. Approximately 5.4 mg of blood cells are captured with close to a tenth of the amount of beads.

Evaluation of H.ER.M.E.S using human samples

We used H.E.R.M.E.S to process blood samples from 15 individuals and analyzed the plasma obtained after extraction (Table 1). We demonstrate an average purity greater than 99.9% (less than 20 cells/µL counted) and an average extraction time of 108 seconds to obtain 90% of the available plasma. H.E.R.M.E.S demonstrates a high efficiency to capture and separate red blood cells irrespective of blood type and hematocrit levels (see supplementary Table S1). To further demonstrate the ability of aggregation to enhance the capture rate, we used

Table 1: Data collected from testing 15 human blood samples with varying ages, hematocrits and blood types. A starting volume of 40 µL was used for each test. Samples were run in duplicate and the standard deviation is reported. Average volume of uncontaminated plasma obtained from centrifugation was 18.2 µL. All samples were purified using 0.625mg of magnetic beads and 200µg of aggregation agent.

Average Purity of Obtained Plasma	**99.95 ± 0.05%**
Average Time for Extraction	**108 ± 21 seconds**
Average Volume Obtained	**17.2 ± 1.96 µL**

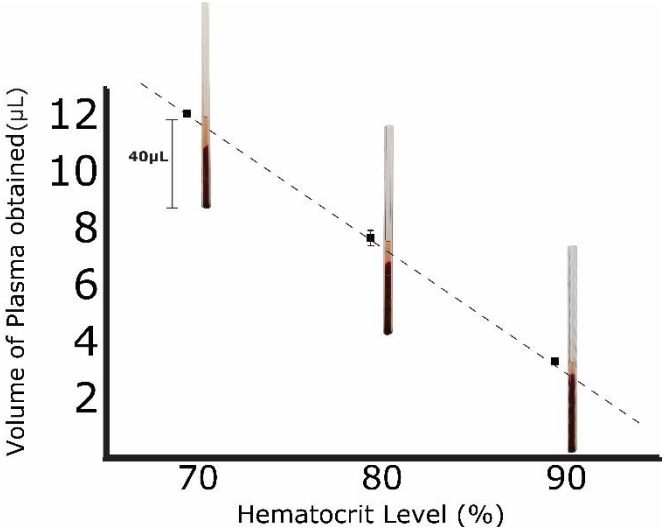

Figure 3: Separation of Plasma from human samples with artificially high hematocrit values. Each sample was tested in duplicate and the standard deviation for each sample set is indicated with error bars (n=2). An average purity of 99.9% was obtained in these samples.

H.E.R.M.E.S to separate erythrocytes in artificially spiked blood samples that have abnormally high hematocrit (Figure 3). We hypothesize that the aggregation effect scales non-linearly with an increase in the number of red blood cells. The high concentration of blood cells decreases the interaction space leading to effective binding in these samples. H.E.R.M.E.S can perform reliably with an increase in red blood cells and is able to obtain highly pure plasma regardless of the number of blood cells. Factoring in the cost of the aggregation agent and the beads, we expect H.E.R.M.E.S to cost less than $2 per separation test (supplementary Table S2).

Quantifying the effect of aggregation on performance

Aggregation reduces the number of effective targets that need to be captured to obtain highly pure plasma. To understand the dependence of the aggregation capabilities on separation performance, we tested the cell capture rate with varying levels of aggregation agent. The cell capture rate was indirectly inferred by calculating the purity of the plasma obtained after separation. We then compared the purity of plasma obtained using different sample volumes to assess the scalability of the technique. As seen in figure 4, it can be noted that a concentration of about 3.5ug/mL of aggregation agent is sufficient to obtain plasma of high purity (greater than 99%). We also observe a non-linear relationship wherein the binding capacity is amplified several-fold as the amount of agent is increased. We expect the curve to be pushed further out in the regime where the concentration of the aggregation agent is low. However, there exists a critical concentration that creates the level of aggregation necessary to obtain highly pure plasma (greater than 99%). In contrast, we also studied the effect of increasing the number of magnetic beads on performance and noted that the amount of beads does not significantly affect the separation of performance.

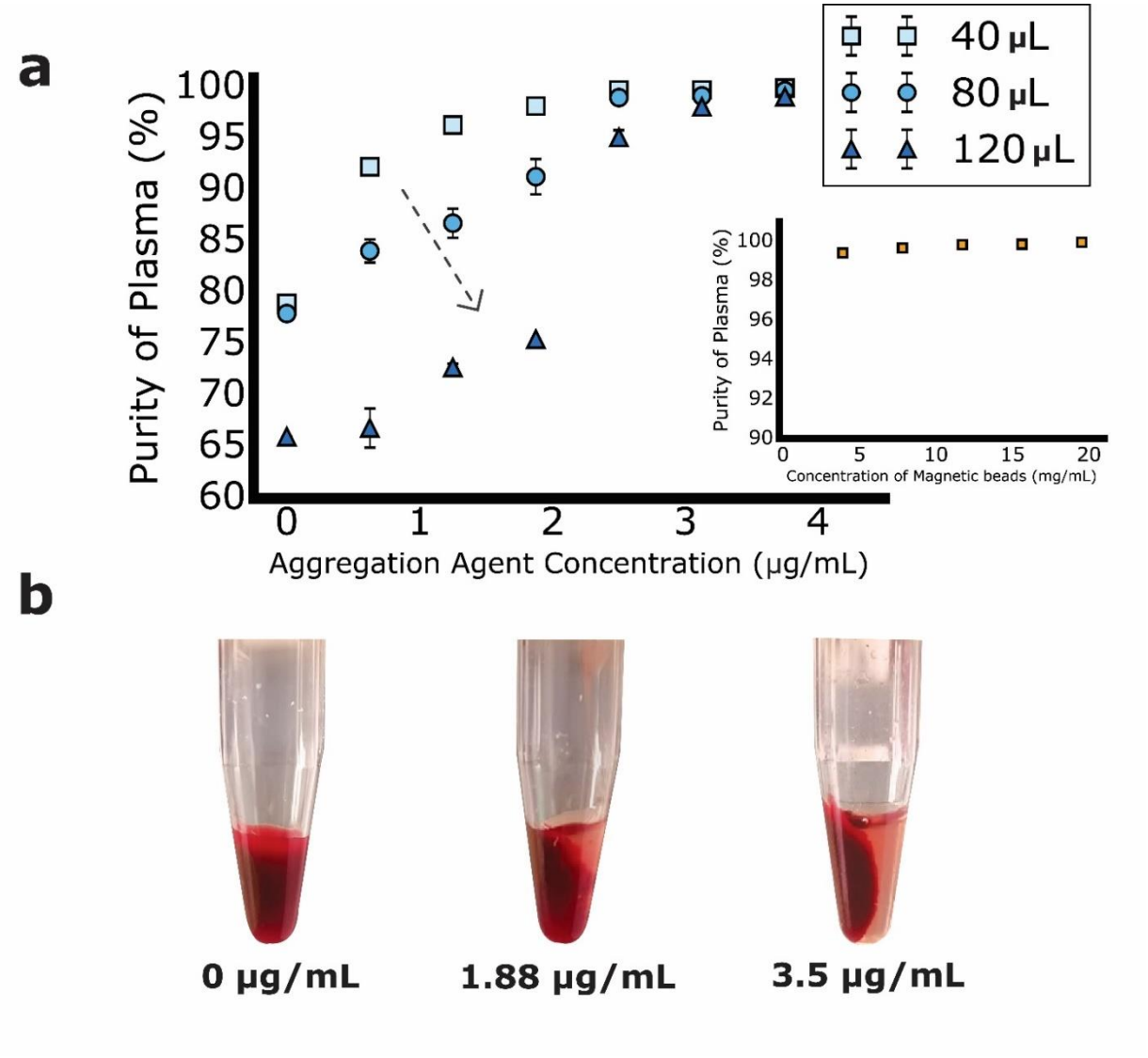

Figure 4: a) Plot showing the effect of the aggregation agent on performance of H.E.R.M.E.S. Three different sample volumes were used *as noted in the legend*. A non-linear relationship is observed between the amount of blood cells and the amount of aggregation agent required to capture them. An average of 34 µL and 53 µL of total recovered plasma were obtained in the cases of samples tested using 80 and 120 µL volumes. Standard deviation for each sample is indicated with error bars. (n=2). The inset shows that the concentration of magnetic beads does not affect the performance significantly b) *I*mages of separated plasma at three different aggregation agent concentrations. From the figure, it is clear that a concentration of around 3.5µg/mL is optimal to obtain highly pure plasma.

variation (6% vs 21%) further proving that it is capable of

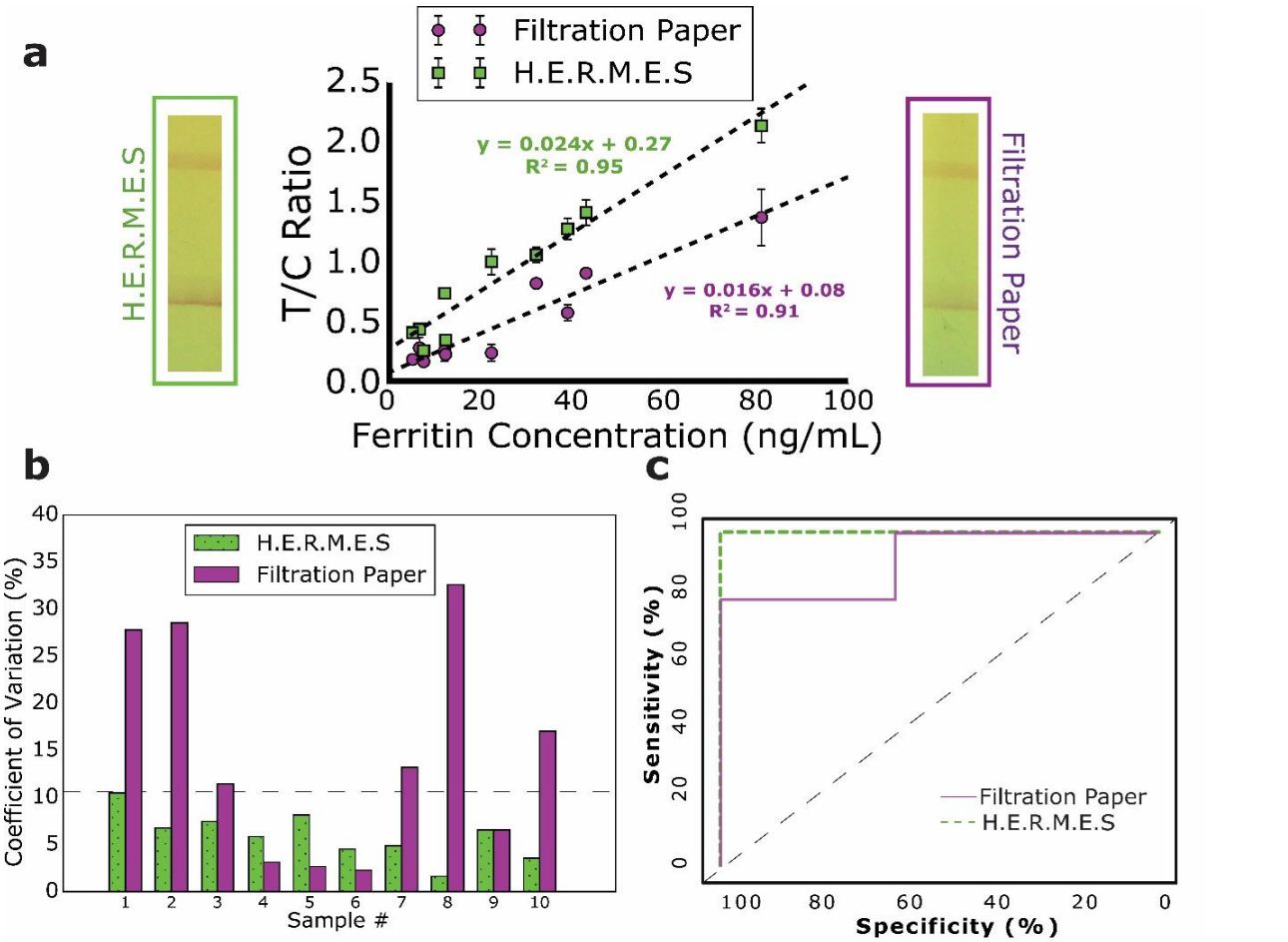

Figure 5: a) Plot comparing the performance of plasma obtained from H.E.R.M.E.S *and* commercially available filtration paper. A starting volume of 40µL was used for each test and 15µL of plasma was used for the strips that were used with H.E.R.M.E.S. The pictures on the left and right side of the plot are images of test strips run using plasma obtained from H.E.R.M.E.S and filtration paper respectively. In general, we note a higher T/C ratio for all the samples that used H.E.R.M.E.S for separation. Further, we observe a higher coefficient of determination R^2 and a sharper slope in the case of samples processed with H.E.R.M.E.S. The standard deviation of each sample (n=2) is indicated by error bars. b) Comparison of the mean coefficient of variations (CV = standard deviation/mean *100) between the two types of plasma. The CV of all samples from H.E.R.M.E.S was lower than 10%. c) Comparison of the ROC curves (generated using the Delong method). The a.u.c from samples purified by H.E.R.M.E.S was 1 and the a.u.c from filtered samples was 0.789.

Integration with existing diagnostic testing platforms

We demonstrate the ability of H.E.R.M.E.S to augment the performance of present day diagnostics by incorporating the technology with lateral flow test strips – a common diagnostic platform often implemented for use at the point-of-need. Ferritin lateral flow strips previously described by Srinivasan et al(28) were tested using 10 human blood samples. We compared the performance of H.E.R.M.E.S against commercially available filtration paper (MDI). A calibration curve was built with a linear trendline fit to compare the performance of the two test cases (Figure 5). In general, we observed that H.E.R.M.E.S leveraged higher quantitative power from the regression model used in each of these cases. ROC curves were plotted using the Delong method(29) and a difference in performance was established. Further, as seen in figure 5 a higher slope (46%) was noted for test strips that incorporated plasma obtained from H. E.R.M.E.S indicating greater quantitative ability across the concentration range of interest. More importantly, H.E.R.M.E.S was able to demonstrate a significantly reduced average coefficient of advancing the performance of point-of-need testing platforms.

Discussion and Conclusion

H.E.R.M.E.S leverages the elementary concept of magnetic separation to carry out a challenging process of separating unwanted cellular material from a sample. The method was specifically designed to be low-cost, rapid and minimally complex. The system was designed to allow for maximal automation and minimal intervention from the user while maintaining a low-cost. These characteristics make H.E.R.M.E.S a promising alternative to the traditional lab centrifuge in settings where a centrifuge cannot operate, whether due to regulatory constraints or resource limitations. Further, while we validated H.E.R.M.E.S with a commonly available point-of-need testing platform (lateral flow tests), it is universal and can be used to simplify purification for virtually any diagnostic test that requires plasma or serum as an input. While there are a handful of sophisticated commercial platforms that are capable of performing immunoassay chemistry without the need for separating red blood cells, H.E.R.M.E.S will enable the use of standard diagnostic techniques in low-resource settings where

other alternatives are not feasible. Further, the high recovery rate (>90% of available serum), the low time for recovery, the low cost and ease of use of the system make it superior to solutions that have been demonstrated in literature. (5,8,30)

H.E.R.M.E.S has the potential to impact the blood testing industry due to its ability to offer the separation efficiency of a centrifuge at a fraction of the time and cost. H.E.R.M.E.S seeks to facilitate the implementation of present-day diagnostic tools at the point-of-need by integrating into CLIA-waived testing environments where centrifuges are currently unable to operate. H.E.R.M.E.S can enable rapid front-end sample processing to help prevent loss of sample quality in these environments by ensuring that all red blood cells are removed prior to clinical chemistry testing. We envision H.E.R.M.E.S having immediate applicability in advancing molecular diagnostics such as PCR to the point-of-need as it can integrate easily in to existing methods for translational PCR. Particularly, the isolation of white blood cells makes an interesting use case for infectious disease detection(31,32) and genetic sequencing(33). In addition to being highly scalable due to the low cost of raw materials that are involved in fabrication, H.E.R.M.E.S is able to perform highly efficient blood plasma separation within 2 minutes at less than $2 per test and is suitable for use in resource-limited settings. While the current iteration of H.E.R.M.E.S is only capable of accommodating one sample, we envision that a future prototype will possess parallel sample processing capabilities as the underlying technique is highly scalable. Further, the stand-alone system is easy to use and can be adopted by users irrespective of their prior medical training making the H.E.R.M.E.S a unique method to perform blood-plasma separation at the point-of-need.

Materials and methods

Preparing Magnetic beads: Magnetic beads (ProMag HP, Bangs Labs) suspended in a 50mM MES Buffer were conjugated to a Anti Red Blood Cell antibody (Rockland Antibodies) by incubating the sample in an end-over-end mixer for 12-15 hours. After conjugation, the supernatant was removed and replaced with a storage buffer (10mM Tris Buffer, pH 8, 0.05% Bovine Serum Albumin, 0.05% Proclin 300). The beads were stored at 4-8°C in liquid form and are stable up to several months. Prior to testing, 325 µg of beads and 200µg of antibody were loaded in a single PCR tube (Eppendorf) and dried in a vacuum centrifuge (Eppendorf Vacufuge 5301) for 30 minutes. The antibody is added separately to induce clumping of the red blood cells to reduce the number of effective targets during the capture process. Dried beads were then used for tests or stored at 4-8°C. The dried beads demonstrated a shelf life of up to three months when sealed in a dark container.

H.E.R.M.E.S benchtop unit: A small portable benchtop unit was designed in Sledworks and printed using a Objet 3D printer. The device itself consists of a microcontroller (Teensy 3.2, Sparkfun), a few transistors and a 12V actuating solenoid (Adafruit Industries). Two circular neodymium magnets (K&J Magnetics) were mounted on a 3D printed holder and attached to the solenoid. The device also has a power input jack that can be connected to standard 12V, 0.5A wall power supply.

Analysis of Plasma: Upon separation of plasma from the red blood cells using H.E.R.M.E.S, a capillary tube (Microcaps, Drummond Scientific) was used to extract the serum from the sample and transferred into another test tube. Once transferred, the serum was diluted 5 times and mixed in a 1:1 ratio with trypan blue stain. Once stained, the serum was loaded into a disposable hemocytometer (C-Chip, Cyto Diagnostics) and cell counting was performed under a bright field microscope. The number of cells counted were then used to estimate the purity of the plasma obtained.

High Hematocrit Samples: Blood samples with abnormal hematocrits were prepared with type O human red blood cells suspended in alsever's solution (Innovative Research). The blood cells were spun down and concentrated in a centrifuge and resuspended to abnormally high hematocrit values (70,80 and 90%)

Lateral Flow Test: Ferritin strips were manufactured similar to work mentioned in Srinivasan et al. We prepared two batches of test strips with blood filtration membranes (Type FR-1(0.35) MDI membrane technologies) used as a sample pad. The FR-1 is a passive forward flowing filtration membrane that has a thickness of 0.35 mm and capacity of 30 µL/cm^2. 10 human blood samples (Innovative Research) were then used for testing. For the strips that used the filtration membranes, a 3-minute incubation period was added at the beginning of the test to allow the plasma to filter through the membrane. This was followed by the application of 40uL of running buffer to start the test. For the test cases that used plasma from H.E.R.M.E.S, the test was immediately started by using a 15µL capillary tube to apply the plasma onto the sample pad followed by application of 40µL of running buffer. We note that these test strips could also have been used as a dipstick format, wherein the sample pad is dipped in the sample holder to start the test. After 30 minutes, the test strips were imaged using the TIDBIT (previously mentioned by Lu et al**(34)**) and a calibration curve was built using custom python code. Actual ferritin values were obtained using a SIEMENS Immulite1000 immunoassay analyzer.

Live Subject Statement: All human samples were purchased from Innovative Research

Acknowledgements

SV and DE would like to thank Vicky Simon in the College of Human Ecology at Cornell University for analyzing the true ferritin values of the sample. They would also like to acknowledge that the device was 3D-printed at the Cornell NanoScale Science and Technology Facility (CNF). **Funding**: Part of this work was funded with NSF award #1343058 and a Cornell University College of Engineering Scale Up and Prototyping Award. **Author contributions:** SV was involved in data collection, data analysis and manuscript and figure preparation. DE contributed to writing and editing the manuscript.

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Table of Contents Entry:

We demonstrate H.E.R.M.E.S, a novel magnetic-bead based method to perform rapid blood-plasma separation at the point of need that can augment the performance of present-day diagnostic testing platforms.