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Microfluidic blood filtration device

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Abstract Rapid decentralized biomedical diagnostics have become increasingly necessary in a medical environment of growing costs and mounting demands on healthcare personnel and infrastructure. Such diagnostics require low-cost novel devices that can operate at bedside or in doctor offices using small amounts of sample that can be extracted and processed on the spot. Thus, point-of-care sample preparation is an important component of the necessary diagnostic paradigm shift. We therefore introduce a microfluidic device which produces plasma from whole blood. The device is inexpensive, reliable, easy to fabricate, and requires only 3.5 kPa pressure to operate. The device is fully compatible with microfluidic diagnostic chips. The output 23-gauge microtube of the former can be directly plugged into the input ports of the latter allowing immediate applicability in practice as a sample-prep prestage to a variety of emergent microfluidic diagnostic devices. In addition, the shown approach of filter encapsulation in elastomer has principle importance as it is compatible with and applicable to microfluidic sample-prep integration with analytical stages within the same elastomeric chip. This can eventually lead to finger-prick blood tests in point-of-care settings.

Keywords Microfluidic · Blood · Filter · Diagnostic · Point-of-care · Sample-prep

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1 Introduction

Microfluidic technology allows for very precise manipulation of minute samples of fluid in controlled environments (Kartalov et al. 2006). Furthermore, microfluidic chips can be mass-produced at low costs (Kartalov et al. 2006) and show potential as small, cheap, and low-powered devices for point-of-care medical testing (Kartalov 2006). Analytical microfluidic devices have already been demonstrated for antigen detection (Henares et al. 2008), viral detection (Cheng et al. 2009), and quantification of various blood protein analytes in human serum (Kartalov et al. 2008) and human plasma (Lin et al. 2009).

However, such devices cannot be used directly with untreated patient samples because they are generally designed to operate with prepared serum or plasma, while the patient can only offer whole blood. As a result, traditional sample preparation techniques (Henderson 1986) have to be employed first, e.g. coagulation and centrifugation for serum, and anti-coagulation and filtering for plasma. Thus, the complete diagnostic procedure cannot be fully miniaturized into a portable point-of-care format until sample preparation is miniaturized as well.

Such miniaturization is complicated due to the fact that serum preparation uses centrifugation to remove the coagulate, a technique that cannot be directly incorporated into a microfluidic chip. The alternative is to filter the coagulate, but this usually results in rapid clogging of the

microfilter. Consequently, researchers have concentrated on the production of plasma on-chip, generally using poly(dimethylsiloxane) (PDMS) (Lee et al. 2003) as the material of choice, as PDMS is inexpensive, disposable, and chemically and biologically inert. The more recent results are encouraging (Moorthy and Beebe 2003, Thorslund et al. 2006, VanDelinder and Groisman 2006, Fan et al. 2008). However, the devices tend to produce only a relatively small amount of sample before becoming clogged (VanDelinder and Groisman 2006), or they leak thrombocytes into the output (Fan et al. 2008), which might interfere with the proper function of the downstream diagnostic assay. In addition, such devices generally consist of filters sealed between layers of PDMS and/or glass, or the filter is defined in the PDMS itself before being assembled to the glass substrate (VanDelinder and Groisman 2006; Fan et al. 2008). These configurations limit the filter surface (due to building the filter perpendicularly to the layer surface) and/or the applicable filtration pressure (due to the danger of sealing failure at the materials' interface in PDMS-glass devices).

Consequently, we have designed and fabricated a microfluidic blood filter tightly sealed within a single molded piece of PDMS. The device is integrated with an anticoagulant ethylene-diamine-tetra-acetic acid (EDTA) coated capillary tube. Whole blood from a single fingertip prick is passed through this tube and through specially-designed filter paper embedded in the PDMS device. The produced plasma exits through a 23-gauge steel microtube, allowing the device to easily interface with other standard microfluidic devices. In comparison to its microfluidic predecessors, the reported device has significantly increased the filtering area, making it less susceptible to clogging and enhancing its filtering capacity. Also, our device makes use of a more efficient filtering material, which further improves its overall filter characteristics. Finally, the complete encapsulation of the filter inside an elastomeric device makes it less susceptible to failure and leakage.

The reported device is also an important demonstration of a fully functional filter encapsulated in elastomeric devices. Such encapsulation allows for sample-prep and analytical devices to be integrated within the same chip, eliminating the dead volume between sub-stages and eventually leading to point-of-care fingerprick blood tests in fully integrated inexpensive analytical systems. The reported device is a technical step towards the future of biomedical diagnostics.

2 Materials and methods

The PDMS blood filter is fabricated using polymer casting around a machined aluminum mold. Figure 1 depicts the

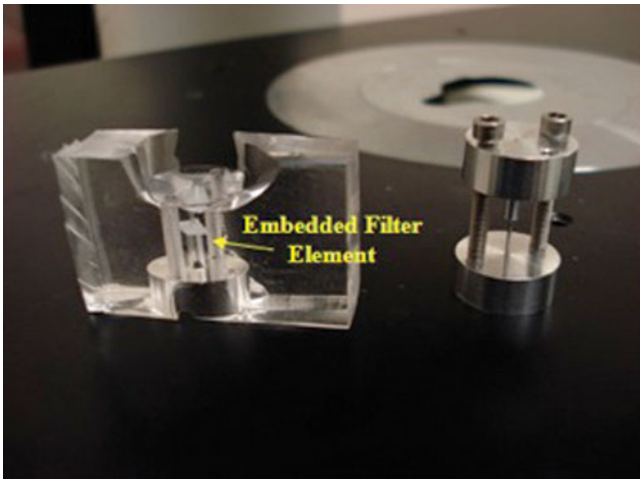

Fig. 1 Aluminum mold and cast PDMS with filter material embedded in the flow channel

mold alongside the finished device. Technical drawings of the aluminum mold are provided as supplemental material. The mold holds a membrane blood filter in place and defines a fluidic circuit between input and output ports compatible with commercially available anticoagulant finger prick blood draw capillary tubes and microfluidic 23-gauge tubes, respectively. The device is cast as a single piece.

A two-piece aluminum replica mold is connected with Allen bolts. The bottom piece contains a 24-gauge steel pin press-fit into the aluminum to mold a hole in the PDMS that seals tightly to the standard 23-gauge tubes typically used in microfluidic devices. The top piece consists of a cylinder designed to mold the PDMS in a fashion such that capillary tubes can be inserted and sealed. The top mold piece contains four holes, two of which are threaded and correspond to tapped holes on the bottom piece. These are used to compress the filter between the top and bottom cylinders, ensuring the creation of a leak-proof channel. The additional two holes are threaded and have no corresponding holes on the bottom piece. These are used to easily back the mold out of the PDMS when the casting process is finished.

The two rounds of the mold, which allow for the capillary tube integration and the 23-gauge pin interface, are connected and serve to compress the blood filter paper. The filter paper is then placed between the top and bottom pins, and Allen bolts are used to secure it in place. There are several inexpensive and readily available filter materials suitable for this device. The BTS-SP series from Pall Corporation (East Hills, NY) was used in fabrication and testing. The BTS-SP media (Fig. 2, www.pall.com) features a highly asymmetric membrane engineered for plasma production from whole blood. The graduated pore structure of the filter consists of larger pores on the upstream side,

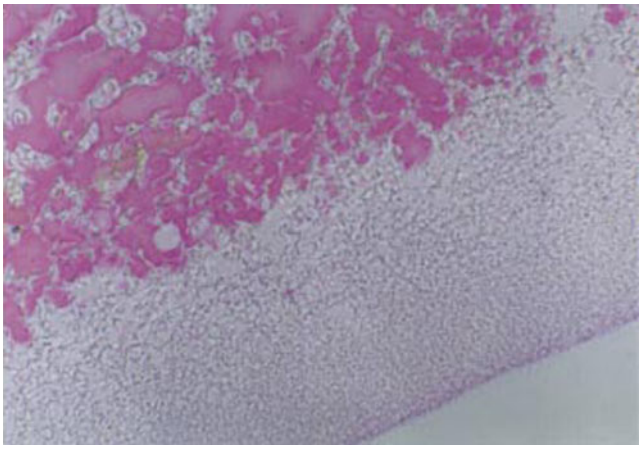

Fig. 2 Micrograph of the BTS-SP filter based on asymmetric polysulfone membranes

with finer pores on the downstream side. This structure allows red and white blood cells to be captured in the larger pores while the plasma wicks into the smaller pores on the downstream side of the membrane. The large pore side of the media served as an absolute cell exclusion zone and performed very well in our device.

The PDMS device is cast in a procedure similar to conventional micro-soft lithography (McDonald et al. 2000). The mold is prepared and placed into a Petri dish. Uncured PDMS prepared in a 10:1 ratio is poured into the dish, covering the mold (McDonald et al. 2000). The dish is left to degas in a vacuum chamber to remove air bubbles from the PDMS mixture. The device is allowed to cure in an 80°C oven for one hour. The cured PDMS is removed from the dish and the device is cut from the underlying PDMS substrate. The Allen bolts holding together the cast

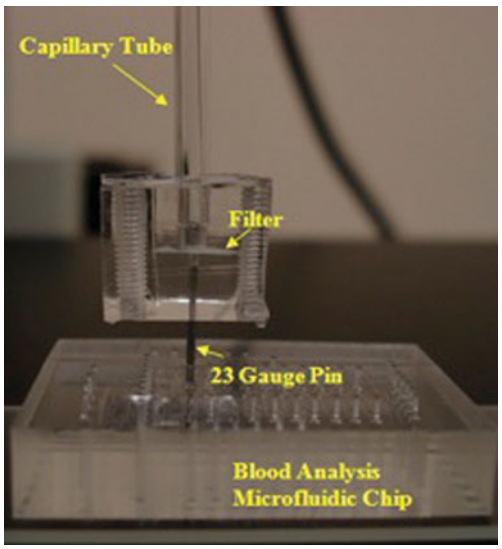

Fig. 3 PDMS blood filter integrated with a blood-draw glass capillary tube and connected to a microfluidic analysis chip through a 23 gauge steel tube

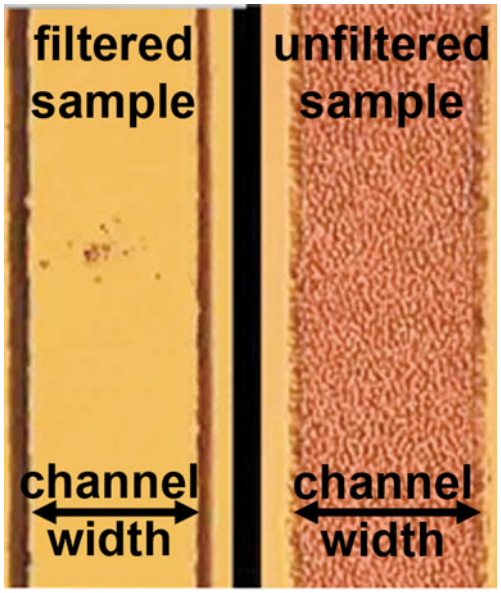

Fig. 4 The comparison between filter output (*left channel*) and unfiltered whole blood (*right channel*) attests to the quality of the filtering. Each channel is 100 μm wide and 10 μm tall

are removed, bolts are inserted into the tapped separation holes, and the mold is slowly backed out of the PDMS. This allows the blood filter paper to remain intact within the microfluidic device.

The choice of capillary tube is specific to the test carried out as different anticoagulants are needed for different analyses. The capillary tube we used (StatSampler Capillary Blood Collectors from StatSpin, Iris Sample Processing, Westwood, MA) had EDTA as an anticoagulant. These capillary tubes are used in medical facilities as a standard finger prick blood draw and are available with several different anticoagulant formulations.

3 Results and discussion

Mouse blood was used to test the effectiveness of the device. Aliquots of the blood sample were stored at 4°C during testing; EDTA was used to prevent the blood from clotting when stored. When testing, 1 mL aliquots of mouse blood were drawn into a blood draw glass capillary tube inserted into the filter (Fig. 3). The blood was forced through the filter under 3.5 kPa of dry nitrogen supplied by a hose attached to the capillary tube. This pressure was chosen to demonstrate that very little pressure is necessary to flow blood through the filter, and the blood filtered through very quickly under these conditions. The filter was able to collect 80 -100% of the available plasma, typically half the total volume of the blood. While microfluidic applications generally require tens to hundreds of nanoliters of plasma for analysis (Kartalov et al. 2008; Lin et al.

2009), our tests demonstrated that this filter was capable of handling a volume of blood large enough for many uses.

The filter was attached to a PDMS device containing a microfluidic channel 100 μm in width and 10 μm in height, through the 23-gauge interconnecting steel tube (Fig. 3). At its upper end, the tube is held tightly by the material of the filter device, while its lower end is held tightly by the material of the analytical device (Fig. 3). Since these are very light structures, additional mechanical support was not necessary. Flow in the channel was imaged with blood both passed through the filter and without the filter. Figure 4 shows the blood sample with and without filtration, demonstrating successful cell elimination. The device filtered more than 2 mL without clogging. Based on our experience, we believe the limit of the current configuration is about 5 mL filtered before clogging.

This design has important advantages over traditional planar microfluidic filters that rely on sealing blood filters between layers of PDMS, or PDMS and a solid substrate. Such devices can effectively use only the thinnest of filters, and require epoxy, thermal or plasma bonding to create tight seals, complicating fabrication and creating concerns of leakage. By contrast, the presented device can use a variety of filtering materials, making the filtering area less limited and increasing the overall reliability and robustness of the device. Finally, the casting method used allows for high reproducibility and low cost of production due to the low cost of PDMS and the reusability of the mold.

In principle, similar filtering systems can be assembled by combining commercial filters with macro-fluidic components, e.g. luer-stub adaptors and connectors. However, each has a dead volume, which leads to losses of sample as a flat initial investment. In contrast, our method can be used to encapsulate the special filter membrane directly inside elastomeric microfluidic devices by design and during the latter's fabrication. The long-term utility of such an approach will be the elimination of dead-volume losses and overall system integration and miniaturization. The result would be diagnostic systems where the sample-prep and the measurement stage are built inside the same disposable device by simple and economic means, while the elimination of many microliters of dead volume would mean the ability to use such devices for fingerprick blood tests in point-of-care settings. Thus, the reported device and approach have important implications for the future of bioanalytical diagnostics.

The system integration described above would also make device fabrication more streamlined, as the process of encapsulation of the filter will be incorporated as part of the industrial fabrication of the overall device. For example, the filter could be sandwiched between consecutive layers in a multi-layer microfluidic chip. Alternatively, the filter can first be encapsulated into an elastomer slab as done here, and then be used as one of the layers in the overall multi-layer chip. Both techniques are fully compatible with modern industrial approaches of microfluidic fabrication, e.g. such as successfully practiced by Fluidigm Corp.

4 Conclusion

We have demonstrated a simple, reliable, and disposable PDMS blood filter device that produces plasma from whole blood while using nominal positive pressure. Casting the device as a single piece ensures leak-free functionality without chemical sealants or complicated bonding procedures. Additional advantages include a larger filtering area, more efficient filtering material, and compatibility with conventional PDMS chips. It contributes as an important sample-prep function to microfluidic diagnostic systems, which promise to shape the future of biomedical diagnostics and healthcare.

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