A Device for Opioid Biomarker Sensing from Interstitial Fluid

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Abstract

In recent years, the over-prescription of opioid medication and the introduction of new synthetics such as illicit fentanyl have led to an opioid epidemic that killed nearly 47,000 Americans in 2018. For accurate and minimally intrusive management of substance abuse, the detection of biomarkers of illicit opioid misuse is critically important. The most commonly used methods are blood drawing and urine sampling, but these can be painful and/or invasive. An alternative source rests in the interstitial fluid (ISF), the extracellular fluid found in the body's tissues. As a result of capillary exchange, ISF contains constituents of the blood that are size-excluded to under ~40-60 kilodaltons.

In order to extract dermal interstitial fluid, we have developed a device that thermally ablates a pore in the stratum corneum, the top layer of flattened, dehydrated skin cells. This flexible and robust device can then collect ISF by autonomous microfluidic transport, induced by the hydrophilic nature of the materials used on the surface of microfluidic channels. The fluid can then be pipette aspirated for off-site biomarker detection with mass spectrometry. Through studying the electrochemical activity of various opioids and opioid metabolites, we aim to determine if on-chip electrochemical detection is compatible with these molecules. This method would allow for the least invasive at-home or in-clinic monitoring of drug dependency.

Identification of biomarkers and development of analytical methods for their detection and monitoring can aid industry in the design and development of innovative diagnostic devices, and the FDA in the assessment of device performance.

Introduction

Addressing the opioid epidemic on an individual patient level is complicated. Urine sampling is disadvantageous because of the intrusive nature of its collection and issues with tampering.

As an alternative, the use of interstitial fluid has been introduced. Human interstitial fluid (ISF) is the extracellular fluid that lies between blood vessels and tissues in the body. Due to capillary exchange, ISF's composition largely mirrors that of blood plasma, but without larger constituents.

Sampling large volumes of dermal interstitial fluid remains a barrier to clinical application. The interstitium is protected by the stratum corneum, the outermost layer of dehydrated, flattened skin cells. Minimally invasive methods developed for accessing the interstitium include laser ablation of the stratum corneum, vacuum blistering, and microneedles, however these each have drawbacks. The former two are difficult to realize on a micro-scale lab-on-a-chip device, and the latter remains invasive & is accompanied by pain response, as penetration into the nerve-containing dermis layer is standard.

We have developed a flexible patch for sampling dermal interstitial fluid by thermal ablation of the stratum corneum. Simple resistive heating elements placed in contact with the skin use a heat pulse to ablates only this outermost layer of skin.

Materials and Methods

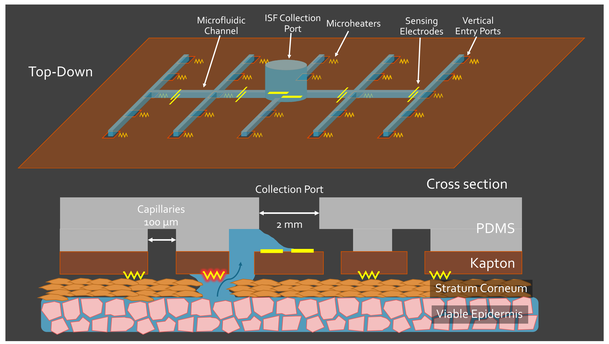


Figure 1. Top-down and Cross-sectional device schematics. These schematics include sensing electrodes for

A device was constructed using standard microfabrication techniques including photolithography, sputtering (CVC), reactive ion etching (Plasmalab 80 Plus), and characterization with scanning electron microscopy (Zeiss SUPRA-55VP).

The device schematic is shown in Fig. 1. The bi-layered device is built on PDMS and Kapton. Kapton makes up the bottom layer which is placed directly in contact with the skin. Microheaters are located on this side of the device. Polydimethylsiloxane (PDMS) makes up the top portion of the device, containing microfluidic channels and a central interstitial fluid collection reservoir.

PDMS was made hydrophilic by addition of the nonionic surfactant-like molecule PDMS-b-PEO (Polysciences). This resulted in a stable hydrophilic surface (Fig. 2(a)). Pictures of hydrophilized PDMS are shown in Fig. 2(b).

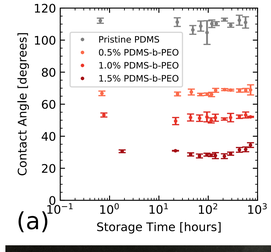
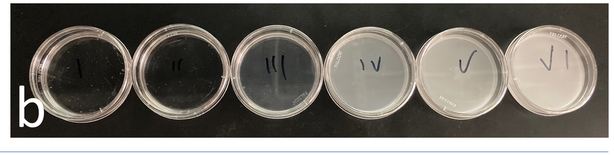


Figure 2. PDMS, inherently hydrophobic, was hydrophilized by adding nonionic surfactants to the pre-cured mixture. These surfactants diffuse to the channels when water (ISF) is introduced, decreasing solid-liquid surface tension and inducing wetting. At high concentrations, the surfactants cause visible wavelength opacity. [(a): O'Brien, *JMEMS 29(5), 2020]*



Results and Discussion

We have successfully pivoted from a prototype device built on rigid and brittle substrates to one fabricated on flexible & conformable polymers, as seen in Fig. 3.

- PDMS microfluidics were fabricated by dropcasting over a HARE SQ-50 negative mold (Fig. 4)
- Microheaters were patterned on a 2 mil (50.8 µm) Kapton sheet (Fig. 5), and 100 µm interstitial fluid entry ports were dry etched through the sheet with an O_2 plasma
- Features on Kapton and PDMS layers were aligned and the surfaces were bonded by functional reactions of self-assembled monolayers on each surface.

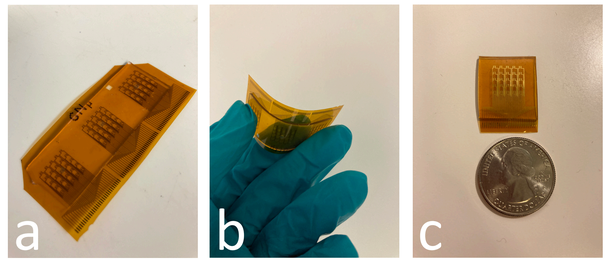


Figure 3. (a) demonstration of the flexibility of three completed devices. Devices can be deformed to adhere to non-planar skin surfaces. (b) Size comparison of a single device with a standard US quarter.

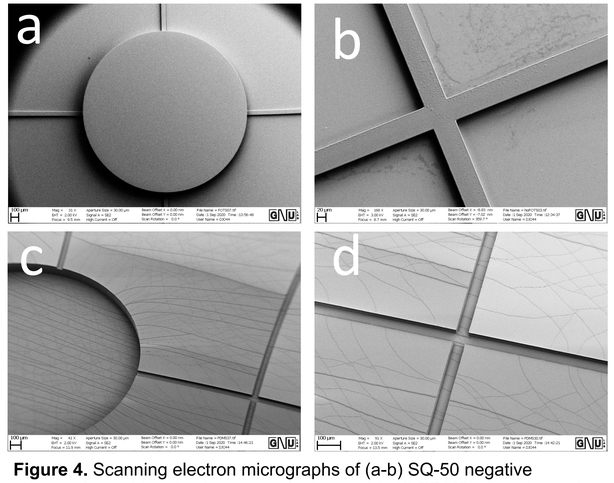


Figure 4. Scanning electron micrographs of (a-b) SQ-50 negative photoresist mold and subsequent dropcasted (c-d) PDMS microchannels.

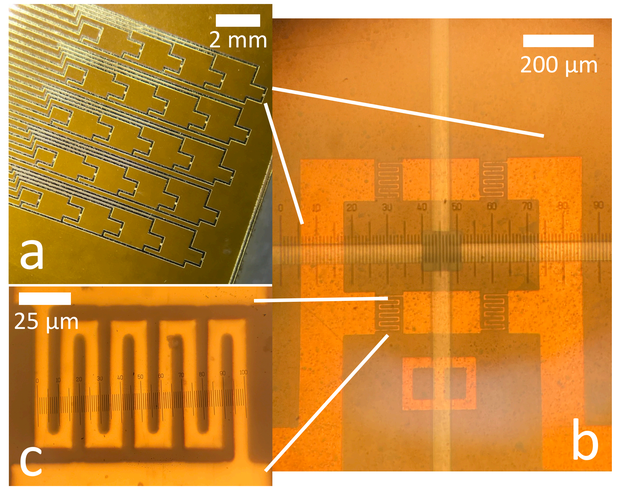


Figure 5. (a) A single device's 5x5 array of sampling sites. Patterned traces are Cr/Au microheaters and electrode leads. (b) A single sampling site, demonstrating four Cr/Au microheaters, a vertical entry port (center black square) etched through Kapton, and PDMS capillaries (long channels running top-bottom and left-right across the sample.

Conclusion

We have modified the fabrication process for an interstitial fluid extraction device to reconcile its design with flexible substrates. The new device is built on PDMS and Kapton, which allow it to conform with the non-rigid shape of the human skin. The device was fabricated with standard CMOS technologies, and is therefore scalable to large volume production.

The device features a collection port for pipette aspiration of interstitial fluid for off-site testing. Alternatively, if testing indicates that opioid monitoring could be carried out electrochemically, sensing electrodes can be added to the device (Fig. 1) on the Kapton sheet opposite the skin.

PDMS was hydrophilized using nonionic surfactants. The long-term stability of this hydrophilization method was demonstrated over a period of 30 days. It is not expected that the stability would deteriorate over longer periods.

Further tests will determine the electrochemical activity of opioid metabolites and the volume of ISF collectable by this device.

The findings of this research, including the challenges in device fabrication and testing, highlight the need for the regulatory science tools which would to facilitate innovation and evaluation of emerging microfluidics device technologies.

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