MICRONEEDLE PATCHES FOR POINT-OF-CARE DIAGNOSTICS

P.P. Samant[1*] and M.R. Prausnitz[1]

[1]School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, USA

ABSTRACT

This paper describes a microneedle skin patch to detect biomarkers in the dermal interstitial fluid (ISF) for point-of-care (POC) diagnostics. The patch has microscopic needles that access dermal ISF by bypassing the stratum corneum and acting as conduits for fluid flow. Fluid flow out of the skin is driven largely by a pressure difference between the ISF and the outside pressure. By applying enhanced pressure gradients, the device can extract microliter quantities of fluid within minutes from ex-vivo pig skin and in-vivo rat skin to be used for further clinical analysis.

KEYWORDS: Microneedle patches, Diagnostics, Point-of-care

INTRODUCTION

POC diagnostics is a rapidly developing industry in an era of decentralized healthcare systems. POC diagnostic devices measure specific biomarker levels in a body fluid in a reliable, accurate and easy-to-use setting. Body fluid sampling is the first step to developing an integrated POC diagnostic device. Conventional sampling techniques are not well suited for a simplified sampling approach. There is a need to develop a simple, easy-to-use sampling platform to extract body fluid. Although dermal ISF is a promising source of biomarkers [1], limitations in existing technology to harvest ISF have constrained its use in commercial diagnostic device.

Microneedles are microscopic needles with dimensions less than one millimeter. Conventionally microneedle patches are used for drug delivery applications [2, 3]. However, they can also access dermal ISF by bypassing the skin's outer barrier layer of stratum corneum and acting as conduits for fluid flow [4]. Since microneedle patches facilitate safer handling and require minimal training, they are well suited for use as diagnostic or monitoring systems that would otherwise require expertise of collecting painful blood samples and clinical testing. Previous attempts to extract interstitial fluid using microneedle patches have been largely unsuccessful because of low extraction rates and/or inaccurate measurements [5-9]. Our goal is to design and build a microneedle patch that can reliably and reproducibly extract a clinically relevant volume of ISF (~1-10 µl) in under 5 min.

THEORY

Microneedles penetrate through the skin's outermost layer, the stratum corneum, to the dermis which is the deepest layer of skin and the central source of dermal ISF. For extraction of ISF, the fluid needs to flow through the skin and out through the microneedles themselves or the pores created by the microneedles up to the skin surface (Figure 1).

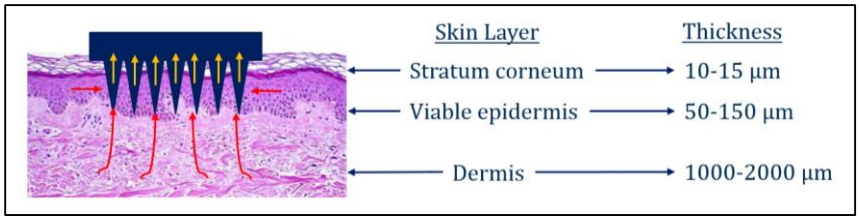

Figure 1: Schematic of microneedles penetrating the skin and the flow of dermal ISF through the skin into the microneedles and then to the skin surface. Reproduced with permission from Pradnya Samant.

This fluid flow is governed by a concentration or pressure gradient. There are several mechanisms of fluid flow – diffusion, capillary force, innate pressure gradient, and externally applied pressure gradient. By calculating estimated flow rates for each of the mechanisms of fluid flow, we previously found that an

externally applied pressure gradient would be the most effective way to achieve a higher flow rate. This study is motivated by these findings.

EXPERIMENTAL

We developed a microneedle patch that reliably and painlessly penetrates the skin. The needles are made from stainless steel and are fabricated by wet-etching lithographically defined patterns in the shape of microneedles. The microneedle patch consists of two layers of metal stainless steel microneedle strips. Absorbent paper is sandwiched in the center and held together by adhesive layers.

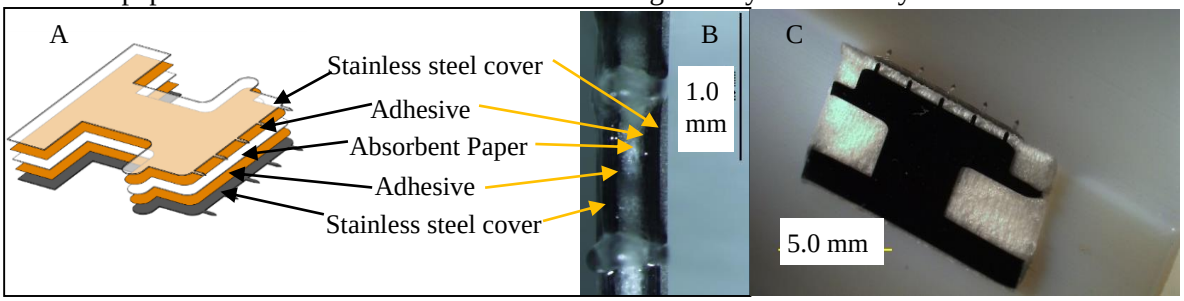

Figure 3: (A) Schematic showing components of microneedle patch with absorbent material sandwiched between 2 layers of stainless steel microneedles held together with adhesive. (B) Cross section of fully assembled microneedle patch. (C) Image of the fully assembled patch. Reproduced with permission from Pradnya Samant.

To extract ISF from skin we tested the patches in ex-vivo pig skin and in-vivo rat skin (with IACUC approval). The patch was inserted into skin and left for 2 min. The patch was taken out and an external transverse force between 0-20 lbf was applied on a 1-2 cm^2 area around the site of the microneedle patch insertion for 2-20 min.

RESULTS AND DISCUSSION

The stainless steel microneedles reliably and reproducibly penetrated the skin. Use of externally applied force was successful in drawing out ISF from both ex-vivo pig skin and in-vivo rat skin compared to no force being applied and use of vacuum to create a negative pressure gradient It is observed that the amount of fluid absorbed is dependent on the amount of force exerted as shown in Figure 4.

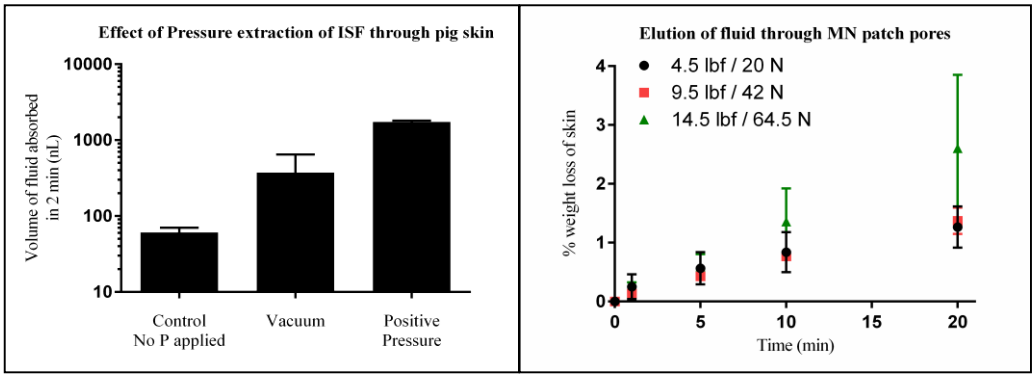

Figure 4: (A) Effect of application of external pressure to draw out ISF against no applied pressure and application of vacuum, (B) Weight loss % of pig skin on application of varying external forces over time. Reproduced with permission from Pradnya Samant.

Extraction of fluid through in vivo rat skin over time is shown in Figure 5. The force applied was 10 lbf. The amount of fluid extracted through in vivo rat skin is lower than that of ex vivo pig skin because rat skin is thinner than pig skin and has lesser fluid content than ex-vivo pig skin saturated with fluid.

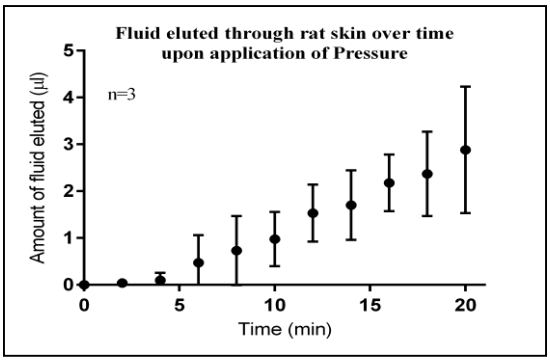

Figure 5: Extraction of ISF from in vivo rat skin. Reproduced with permission from Pradnya Samant.

CONCLUSION

We have demonstrated that we can extract clinically relevant volumes of interstitial fluid through skin in a reproducible manner using a novel microneedle patch. After additional development and characterization, this device can be integrated with other microfluidic devices for analysis that can be adapted to continuous or time-averaged measurements.

ACKNOWLEDGEMENTS

We would like to acknowledge the contribution of Dr. Eric Felner, our collaborator at Emory School of Medicine and our funding agencies NIH, Children's Healthcare of Atlanta and Perm State University. We would also like to acknowledge Joshua Palacios and Ant Yucesoy for their invaluable contribution to design of the device and assistance with experiments. Mark Prausnitz is an inventor of patents that have been licensed to companies developing microneedle-based products, is a paid advisor to companies developing microneedle-based products, and is a founder/shareholder of companies developing microneedle-based products. The resulting potential conflict of interest has been disclosed and is managed by Georgia Tech and Emory University.

REFERENCES

1. Kool, J., et al., *Suction blister fluid as potential body fluid for biomarker proteins.* Proteomics, 2007. **7**(20): p. 3638-50.
2. Prausnitz, M.R. and R. Langer, *Transdermal drug delivery*. Nat Biotechnol, 2008. **26**(11): p. 1261-8.
3. Prausnitz, M.R., S. Mitragotri, and R. Langer, *Current status and future potential of transdermal drug delivery*. Nat Rev Drug Discov, 2004. **3**(2): p. 115-24.
4. El-Laboudi, A., et al., *Use of microneedle array devices for continuous glucose monitoring: a review*. Diabetes Technol Ther, 2013. **15**(1): p. 101-15.
5. Wang P.M., C.M., Prausnitz M. R., *Minimally invasive extraction of Dermal Interstitial Fluid for Glucose Monitoring using Microneedles.* Diabetes Technology and Therapeutics, 2005. **7**(1): p. 131-141.
6. Donnelly, R.F., et al., *Hydrogel-Forming Microneedle Arrays for Enhanced Transdermal Drug Delivery*. Adv Funct Mater, 2012. **22**(23): p. 4879-4890.
7. Corrie, S.R., et al., *Surface-modified microprojection arrays for intradermal biomarker capture, with low non-specific protein binding.* Lab Chip, 2010. **10**(20): p. 2655-8.
8. Jina, A., et al., *Design, Development, and Evaluation of a Novel Microneedle Array-based Continuous Glucose Monitor.* J Diabetes Sci Technol, 2014. **8**(3): p. 483-487.
9. Mundy L., et. al., *GlucoWatch G2 Biographer for the non-invasive monitoring of glucoselevels*, in *National Horizon Scanning Unit Horizon scanning report*. 2004, Australia and New Zealand Horizon Scanning Network: Canberra, Australia. p. 1-28.

CONTACT

*** Pradnya Samant; phone: +1-404-956-1805; ppsamant@gatech.edu**