Measuring Microneedle Penetration into Skin using DIC and Micro-CT

R. Joyce[1a], S. Evans[1a], K. Rankin[2] , M. Potts[1a], S. Coulman[1b], J. Birchall[1b] and R. Pullin[1a]

[1a]School of Engineering, Cardiff University, UK, [1b]School of Pharmacy, Cardiff University, UK,

[2]μVis, Faculty of Engineering and Physical Sciences, University of Southampton, UK

[a]JoyceR3@Cardiff.ac.uk

Abstract.
Microneedles have the ability to offer safe and painless delivery of therapeutics into the skin, but despite many attempts it has proved difficult to ensure reliable skin penetration. The aim of this study is to measure and simulate the penetration of microneedles into a skin substitute to improve the understanding of skin deformation during indentation and subsequent penetration of microneedles. Two experimental methods are presented to image and calculate the deformation and puncturing of a skin substitute (silicone), Digital Image Correlation (DIC) and micro-focus computed tomography (μ-CT). Initial results show that DIC can provide localized displacement and strain measurements around the needle, although due to the curvature of the silicone surface, it is difficult to see the region around the very tip of the needle. Future studies will investigate the deformation using scaled needles, imaging microneedle penetration into silicone using μ-CT and further FEA (Finite Element Analysis) improvement for surface displacement validation.

Introduction

Transdermal drug delivery offers promising advantages over conventional hypodermic needles to deliver therapeutics into the skin. Transdermal patches of microneedles (MNs) provide painless insertion and can be administered by hand without the need of trained medical personnel. MNs pierce the top layer of the skin, the epidermis, without reaching the nerves and blood vessels within the lower dermis. The introduction of microchannels into the skin excludes the limitations the stratum corneum imposes on most drug compounds such as vaccines, creams, and insulin. The fundamental understanding of the relationship between microneedles and skin during the deformation process has been hindered by experimental methods available. Visualizing and imaging the penetration of microneedles has proved difficult, with many methods unable to accurately see the full insertion process. Experimental measurements of strain across the surface of skin, or skin substitutes, are valuable to validate FEA models. Displacement maps from DIC measurements can be compared to FEA results and used to assess the accuracy of the constitutive models used to represent the skin and potentially to identify the material parameters. On the other hand, μ-CT images the entire 3D volume of a sample and hence can be used to measure deformation of deeper structures in the skin as the needle penetrates. Whilst μ-CT is designed to image static objects, repeated images at small displacement increments can be used to image the deformation of the material as the microneedle passes through it. This method has the potential to show details of microneedle puncturing that have never previously been imaged. The aim of this study is to use DIC and μ-CT to measure the deformation and failure of the skin as a needle penetrates, initially using silicone as a skin substitute.

Methodology

The MN was manufactured from stainless steel using wire EDM, with dimensions 1.1x0.3x1.5mm. Scaled single needles were fabricated from stainless steel 10x and 100x bigger than the original MN (11mm and 110mm length respectively).

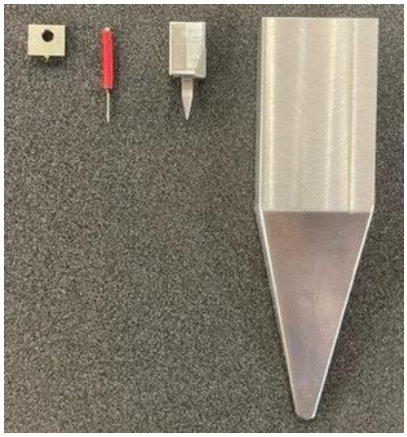

Figure 1 – comparison of the MN, DIC needle, x10 and x100 scaled needle

For DIC measurements, two cameras (Limess.com) with lenses (Schneider-Kreuznach Xenopian 20/28/0901), and 10mm extension tubes were 50mm apart and approximately 65mm from the silicone specimen. These

were used to record the surface of the silicone during a test on a servohydraulic testing machine (Losenhausen, with an MTS FlexTest GT controller) with a 10N load cell (Interface). Silicone (Technovent Teksil 25) was mixed with a ratio 9:1 Part A (90g) to Part B (10g) and cast in a mould with diameter 100mm and depth of 10mm. Using a vacuum chamber (DVP Technology) the silicone was degassed at -1bar for approximately 10 minutes and subsequently cured for 24 hours. A speckle pattern of white and black face paint (Snazaroo) was applied using a sponge onto the surface.

For μmicro-CT imaging, titanium dioxide particles were added to the silicone to provide unique fiducial markers throughout the volume with sufficient contrast, size and distribution to allow image registration. A 4:1 silicone (5g) to titanium dioxide particle (1.25g) mix was fabricated, the titanium dioxide has an average particle size of 10 microns with larger agglomerates throughout the mix. The titanium dioxide particles were initially mixed by hand, then mixed in a speed mixer (Hauschild DAC800.1 FVZ) at 18000rpm for 8 minutes before degassing. The silicone was then μ-CT scanned at 110 kVp 10W using a 160 kVp Zeiss Xradia Versa 510 (Carl Zeiss GmbH, Germany) at 1 μm voxel resolution. Reconstructed volumes were processed in Fiji/ImageJ [1] for assessment of particle distribution for subsequent correlation

To complement the DIC and μ-CT experiments an FEA model of the silicone and microneedle was created using FEBio (www.febio.org), a non-linear finite element software that is specifically designed for biomechanics [2]. A quarter model of the silicone, of dimensions 0.5x1x1mm, was used with the assumption that the model is symmetric about two planes. A 4-node tetrahedron mesh was developed within Salome 9.7 and imported into FEBio, with a mesh distribution designed so that the element density was greater where the needle tip interacts with the silicone.

Results

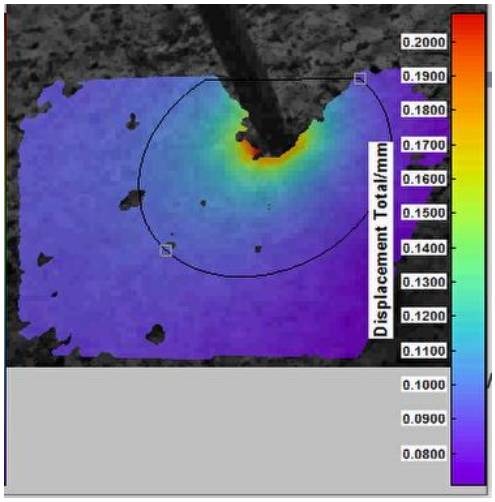

Figure 2 – Displacement across the silicone at 0.5mm penetration

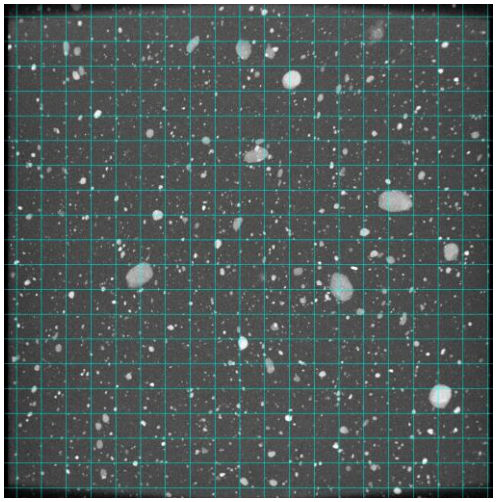

Figure 3 –maximum intensity projection of 100 μ-CT slices dispersion of titanium dioxide through silicone

Figure 2 depicts the displacement across the silicone surface at approximately 0.5mm of penetration. Because of the curvature of the surface, it is difficult to see the region around the very tip of the needle. Figure 3 shows the maximum intensity projection of 100 μ-CT slices, showing the variation of titanium dioxide particles dispersed through the silicone within 100x100 pixel regions.

Discussion and conclusion

Presented within this work is the initial displacements and deformation of silicone during a dynamic needle penetration of 0.5mm. The initial results show a lack of data close to the needle tip which is most likely linked to the camera distance and angle to the silicone and needle. μ-CT imaging shows the dispersion of titanium dioxide, which can be improved upon by breaking up the larger agglomerates. This silicone mix will then be used to image a microneedle penetrating the silicone with the hopes that greater detail surrounding the mechanical behaviour during insertion can be imaged. The displacement data collected from both experiments will be used to validate computational models which has applications in the future improvement of microneedle design.

References

[1] Schindelin, J., Arganda-Carreras, I., Frise, E., Kaynig, V., Longair, M., Pietzsch, T., … Cardona, A. (2012). Fiji: an open-source platform for biological-image analysis. *Nature Methods*, *9*(7), 676–682. doi:10.1038/nmeth.2019

[2] Maas SA, Ellis BJ, Ateshian GA, Weiss JA. FEBio: Finite Elements for Biomechanics. *J Biomech Eng* 2012;134(1):011005.