Development of Novel Microneedle-based Systems for the Minimally Invasive Monitoring of Neonates

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ABSTRACT SUMMARY

Here we propose a unique microneedle (MN)-based system for the blood-free drug monitoring of neonates. Application of the system in the skin results in swelling of microneedles due to the uptake of cutaneous interstitial fluids. The device is withdrawn intact from the skin and the extracted fluids analyzed for drugs and analytes of interest.

INTRODUCTION

Around 1 in 8 babies born in the UK are admitted to a neonatal unit because of an infection¹. Due to their vulnerability and the associated complications, these patients are frequently treated with multiple drugs. However, due to the substantially different dose requirements compared to older children, close and accurate drug monitoring of neonates is necessary. Unfortunately, direct blood sampling can cause severe bruising or scarring and neonates have a limited blood supply, which prevents frequent sampling. Interstitial fluid concentrations often accurately reflect free (unbound and hence pharmacologically-active) concentrations of drugs substances in plasma, with tissue concentrations being usually more predictive of clinical outcome than total plasma concentrations². However, the stratum corneum barrier, the outermost layer of the skin, prevents efficient outward migration of body fluids. A suitable technique is therefore required to extract sufficient quantities of interstitial fluid for subsequent analysis. Microneedle (MN) arrays are miniaturized devices, which are able to by-pass the stratum corneum barrier, without impinging on the underlying blood vessels and nerve fibres. MNs are therefore minimally invasive as they can be inserted into the skin without causing pain and bleeding. Unique hydrogel-forming MN arrays, prepared from cross-linked polymers, have been developed in our laboratories. Once applied to the skin, the MNs swell rapidly due to uptake of skin interstitial fluids. Such MN design has been shown to enhance transdermal diffusion of drugs from an integrated patch reservoir through the swollen MNs³. Alternatively, in the current study, we seek to exploit this MN design as a means to extract skin interstitial fluids for subsequent analysis of therapeutic molecules and diagnostic markers.

EXPERIMENTAL METHOD

Hydrogel-forming MNs (height = 600 µm, width at base = 300 µm, interspacing = 300 µm, 19x19 arrays, baseplate area = 1 cm²) were prepared from aqueous blends containing 15% w/w poly(methylvinylether/maelic acid) and 7.5% w/w poly(ethyleneglycol) 10,000 by using laser-engineered silicone micromould templates. MNs were crosslinked (esterification reaction) by heating at 80°C for 24 h. The appearance of MNs was characterized by scanning electron microscopy (SEM).

MNs were inserted to the ventral forearm of 4 healthy human volunteers. Each subject received 5 MN arrays, which were applied and removed after 1 h, 2 h, 3 h, 10 h and 24 h. Following MN withdrawing, the degree of interstitial fluid uptake was determined by measuring the weight variation of the MN arrays at the specified application times.

Optical coherence tomography (OCT) was used for real time visualization of MN insertion in human volunteers. Moreover, surface-enhanced Raman spectroscopy was used to evaluate the capability of MNs to extract the drug theophylline (currently used for the treatment of apnoea in neonates) from simulated interstitial fluids in vitro.
RESULTS AND DISCUSSION

Figure 1 depicts the appearance of representative hydrogel-forming MNs imaged by SEM (A, B). Successful interstitial fluid uptake was indicated by the increased dimensions of the swollen MNs (B) in comparison to intact MNs (A) following skin insertion. OCT showed consistent MN penetration into skin in human volunteers (C).

![Figure 1. Laser engineered, micromoulded, MN array prepared from aqueous blends of co-polymer poly(methylvinylether-co-maleic acid) and the crosslinker poly(ethyleneglycol) 10,000 daltons (A). Swollen, cross-linked poly(methylvinylether-co-maleic acid) microneedles prepared in our laboratory (B). Optical coherence tomography showed uniform microneedle penetration into the viable epidermis (C). Scale bar (B) = 100 µm, (C) = 300 µm.](image)

Quantitative analysis of interstitial fluids retained by MN arrays following insertion into human skin in vivo revealed a consistent increase of fluid uptake at longer application times (Figure 2). Determination of the dose of theophylline retained by MNs from simulated interstitial fluids indicated that concentrations of medicament in the low microgram range (i.e. ~18 µg/ml) could be accurately detected by the methodology employed. Efforts are under way to further improve extraction and detection of a wide range of analytes so as to maximise applicability to neonatal monitoring.

CONCLUSION

Hydrogel-forming MN arrays are able to penetrate human skin uniformly and rapidly retain interstitial fluids. The therapeutic molecule theophylline, currently used for the treatment of neonatal apnoeas, could be retained by MNs and detected by our methodology. MNs produced in our laboratories offer the potential to overcome the limitations associated to conventional drug sampling in neonates by allowing frequent and minimally-invasive drug monitoring.

REFERENCES


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