Rapidly – Dissolvable Microneedles for Transdermal Delivery via a Highly Reproducible Soft Lithography Approach

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ABSTRACT SUMMARY
Microneedle devices are an attractive method to overcome the epidermis and effectively transport therapeutics transdermally. The fabrication of highly reproducible polymer microneedles is described. These completely dissolvable microneedle arrays are made on flexible substrates using PRINT. Devices showed efficacy in piercing the skin and delivering a fluorescent drug surrogate to both ex vivo murine and human samples.

EXPERIMENTAL METHODS
To fabricate PRINT microneedle patches, master templates were first prepared using a tilted-rotated photolithography approach. First, a polished silicon wafer was coated with thin an anti-reflective layer. A thick layer of negative photoresist (SU-8) was administered via spin coating and a mask (200 µm x 200 µm squares with 200 µm base-to-base spacing) was applied. The complex was exposed to UV light at incidence angles of 18-25°; the wafer was then rotated 90° about the surface normal for a total of four exposures. The resulting square pyramidal cavities were 360 µm deep and had tip radii of curvature under 10 µm, seen via Environmental Scanning Electron Microscopy (ESEM).

A positive replica of the master template was made using polydimethylsiloxane (PDMS) as an intermediate. A thick PDMS layer was cast upon the master, centrifuged at 3000g, and cured overnight at 25°C. The positive replica was then used to make PRINT-compatible molds from a photocurable perfluoropolyether (PFPE) elastomer. A 0.2 wt% solution of 2,2-diethoxyacetophenone in PFPE was cast onto the replica and cured in a UV oven. The resulting molds are consistent with the dimensions of the replicas, reproducibly mimicking the SU-8 master templates.

Microneedles were fabricated using an adapted PRINT process. Films of polyvinylpyrrolidone (PVP) were loaded with 0.1% rhodamine B fluorescent dye. A film was mated to the PFPE mold and passed through a heated nip at 105°C, filling the mold with discrete microneedles. The filled mold was mated to a flexible, water-soluble substrate (made from a blend of Plasdone, a polyvinylpyrrolidone/polyvinylacetate blend, and triethyl citrate) and passed through a heated nip at 65°C. The mold was then removed, leaving a 100% water soluble microneedle patch. Microneedle morphology was confirmed via ESEM and brightfield macroscopy.

Microneedle patches were tested on ex vivo nude murine skin and human skin (obtained via the Cooperative Human Tissue Network). Flexible PRINT microneedle patches were “rolled” on with gentle force of thumb and remained in the skin for a duration of either 10s or 10min. For the 10s tests, the patch backing was removed and the skin was exposed to green tissue-marking dye for 5min. For the 10min tests, the patch backing was then dissolved with <200 µL of tap water. All skin samples were fixed for 2h in 2% paraformaldehyde and left overnight in 15% sucrose in 1X PBS at 4°C. Control skin samples were also prepared; these samples were not exposed to microneedles.
Tested murine and human skin samples were embedded in Optimum Cutting Temperature medium and cryosectioned. Sections (12 µm) were taken at -25°C. Half of the sections imaged via fluorescent microscopy. The remaining sections were hematoxalin and eosin (H&E) stained for brightfield microscopy imaging. Staining was done using the procedure outlined by Cancer Diagnostics for their CRYO-KIT prior to coverslipping.

RESULTS AND DISCUSSION

Master templates, replicas, molds and PRINT microneedles are shown in Figure 1A-D. The microneedles retained the dimensions of the master with remarkable reproducibility. The flexibility of the array can be seen in Figure 1E-F. The rigid microneedles remained intact after the gentle bending of the array by hand. Both the microneedles and the substrate were seen to dissolve rapidly (~5 min) in the presence of a few drops of water. Therefore, novel 100% water-soluble microneedle patches on flexible substrates can be made quickly and reproducibly via PRINT processing.

The optimized PRINT microneedle arrays were first tested in ex vivo murine skin samples (see Experimental Methods). After H&E staining and brightfield imaging, the control samples did not show any epidermal breach as expected (Figure 2A); the skin was consistently smooth. Evidence of epidermal breach was seen in skin sections from both testing conditions (Figure 2B-C). Images of the unstained skin via fluorescent microscopy showed the efficiency of the drug surrogate delivery. Seen in Figure 2D-F, a large qualitative difference in fluorescence intensity was observed among the three samples. While the control showed no fluorescence (Figure 2D), an observable fluorescence was seen in the 10s test in selective areas of the skin (Figure 2E). Comparatively, considerably higher fluorescence intensity within the skin was seen for the 10min time period throughout the whole skin section (Figure 2F). This confirms that the drug surrogate was released from the needles and diffused beneath the stratum corneum throughout the duration of the patch application.

CONCLUSION

PRINT microneedle arrays (100% water-soluble) were fabricated on flexible substrates. These arrays were efficacious in piercing skin and delivering drug surrogate.

REFERENCES


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