Two Photon Polymerization of Microstructured Medical Devices

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Statement of Purpose: One promising option for delivery of pharmacologic agents involves the use of microneedles (Park JH. J Controlled Release. 2005:104:51-66). By reducing the dimensions of the device, damage at the injection site and pain to the patient may be diminished. Hollow microneedles may allow transport of pharmacologic agents to be adjusted over an extended period of time (Griss P. J Microelectromech S. 2003:12:296-301). Metallic and ceramic microneedles prepared using many conventional microelectronics fabrication techniques do not exhibit sufficient skin penetration or fracture properties for clinical use.

We have used two photon polymerization (2PP) to create microneedle arrays for transdermal drug delivery (Narayan RJ. Acta Biomater. 2006:2:267-275; Ovsianikov A. Int J Appl Ceramic Technol. in press). The two photon polymerization process involves spatial and temporal overlap of photons to bring about chemical reactions leading to photopolymerization within well-defined highly-localized volumes. The absorption of laser pulses breaks apart chemical bonds on starter photoinitiator molecules within a small focal volume. The radicalized starter molecules react with monomers and create radicalized polymolecules. The desired three-dimensional structure is produced by polymerizing the material along the laser trace, which is moved in three dimensions using a micropositioning system. Two photon polymerization provides several advantages over conventional processing for scalable mass production of microneedles. A large variety of inexpensive ceramics, polymers, and other photosensitive materials may be used for two photon polymerization. In addition, two photon polymerization can be set up in a conventional “dirty” manufacturing environment that does not contain cleanroom facilities. Finally, two photon polymerization of microneedles is an extremely rapid, straightforward, single-step process, as opposed to conventional multiple-step fabrication techniques.

Methods: Three-dimensional microneedle arrays were produced by two photon polymerization of Ormocer® US-S4. Ormocer® US-S4 is a ultraviolet light-sensitive material that exhibits a refractive index of 1.520 at λ=589 nm. These amorphous hybrid materials were originally prepared by the Fraunhofer-Institut für Silicatforschung (Wurzburg, Germany), and are produced using sol-gel processes from liquid precursors. These materials include urethane- and thioether (meth)-acrylate alkoxysilanes, and contain strong covalent bonds between the ceramic and polymer components. The crosslinking of inorganic and organic moieties leads to the formation of a three-dimensional network, which provides Ormocer® material with significant chemical and thermal stability. The Irgacure® 369 initiator (Ciba Specialty Chemicals, Basel, Switzerland) has an absorption peak at around 320 nm. Femtosecond laser pulses (60 fs, 94 MHz, < 450mW, 780 nm) from a titanium: sapphire laser (Kapteyn-Murnane, Boulder, CO) were focused using a 10 x conventional plan achromat microscope objective into a small focal volume within the photosensitive resin. Cell proliferation on Ormocer® surfaces processed using two photon polymerization was examined using human epidermal keratinocytes. 3-(4, 5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide (MTT) testing was performed using a modification of the Mossman method.

Results/Discussion: The flexibility of the two photon polymerization process allows rapid fabrication of microneedles with different designs. In-plane hollow microneedle arrays and out-of-plane hollow microneedle arrays in various geometries were fabricated using two photon polymerization. The length of the microneedles (800 μm) would enable use for both delivery of pharmacologic agents and drawing of blood and/or interstitial fluids. Off-center microneedles were fabricated by adjusting the position of the channel relative to the central symmetry axis. Both the control surface and Ormocer® surface were shown to support human epidermal keratinocyte growth. The MTT human epidermal keratinocyte viability results indicate that human epidermal keratinocyte growth on the Ormocer® surfaces was similar to that on control surfaces (> 95%). In addition, these growth values were not significantly different ($p<0.05$). These results suggest that Ormocer® materials processed using two photon polymerization do not impair cell viability or cell growth.

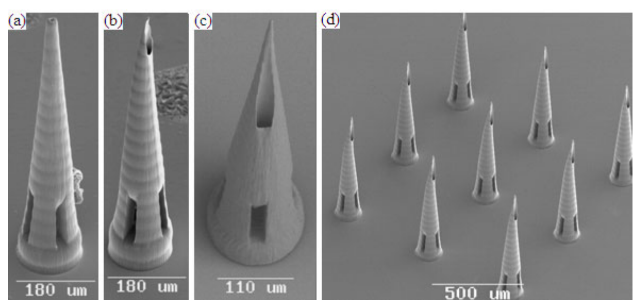

Figure 1. (a-c). Scanning electron micrographs of in-plane and out-of-plane microneedles with various aspect ratios. (d). Scanning electron micrograph of microneedle array.

Conclusions: Our results suggest that two photon polymerization is able to create in-plane and out-of-plane hollow Ormocer® microneedles with a larger range of geometries than conventional microfabrication techniques.