Laser-Based Rapid Prototyping of Microstructured Medical Devices

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Statement of Purpose:
A novel laser-based rapid prototyping technique known as two photon polymerization has been developed for fabricating microstructured medical devices. In this study, two photon polymerization was used to fabricate microscale devices known as microneedles for transdermal drug delivery. Microneedle devices were fabricated from Ormocer®, an amorphous organic-inorganic hybrid material containing organically modified silicon alkoxides, metal alkoxides, and organic monomers. Two photon polymerization provides several advantages over conventional lithography-based techniques for scalable mass production of microneedles and microneedle arrays. A large variety of inexpensive, readily available polymers and other photosensitive materials may be processed using two photon polymerization. Two photon polymerization can be set up in a conventional manufacturing environment that does not contain specialized cleanroom facilities. Finally, two photon polymerization of microneedles is an extremely rapid, single-step process, as opposed to conventional multiple-step lithography-based techniques. Mechanical, cell proliferation, and transdermal delivery studies were conducted on microneedles and arrays of microneedles fabricated using two photon polymerization.

Methods:
Two photon polymerization was used in order to fabricate individual microneedles and microneedle arrays for transdermal drug delivery using Ormocer® organically modified ceramic materials. Ormocer® US-S4 is light-sensitive material that exhibits a refractive index of 1.520 at a wavelength of 589 nm. Ormocer® organically modified ceramic materials are hybrid materials that were originally prepared by the Fraunhofer-Institut für Silicatforschung (Wurzburg, Germany); these amorphous materials are produced using sol-gel processes from liquid precursors. Interactions between inorganic and organic components in Ormocer® materials lead to the formation of a three-dimensional network that provides these materials with chemical and thermal stability. The Irgacure® 369 initiator (Ciba Specialty Chemicals, Basel, Switzerland) demonstrates an absorption peak at ~320 nm.

Two photon polymerization is a rapid prototyping process that involves spatial and temporal overlap of photons from a Ti: sapphire femtosecond laser to bring about chemical reactions leading to photopolymerization within well-defined and highly-localized volumes [1-2]. In the two photon polymerization process, temporal and spatial overlap of photons from femtosecond laser pulses takes place. The absorption of photons from femtosecond laser pulses breaks apart bonds on photoinitiator molecules within a small focal volume. Radicalized photoinitiator molecules react with monomers in order to create radicalized polymolecules. Photopolymerization and hardening of Ormocer® material occurs within well-defined and highly-localized volumes. A microneedle with an arbitrary geometry may be produced by polymerizing the Ormocer® material along the laser trace, which is moved in three dimensions using a microscale positioning system. 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 focal volume within the unpolymerized Ormocer® solution. Cell proliferation on Ormocer® surfaces was determined using commercially obtained human epidermal keratinocytes. Cadaveric porcine skin was used for compression and transdermal delivery studies

Results / Discussion:
The flexibility of the two photon polymerization process enables rapid fabrication of microneedles with a variety of designs. In-plane hollow microneedle arrays and out-of-plane hollow microneedle arrays with several geometries were created using two photon polymerization. The lengths of the microneedles (800 μm) enable use for both delivery of pharmacologic agents and withdrawal of biological fluids for in situ sensing. Off-center microneedles were fabricated by adjusting the location of the channel relative to the highest point of the needle. An MTT assay indicated that human epidermal keratinocyte growth on the Ormocer® surfaces was similar to that on control (polystyrene) surfaces. These results suggest that Ormocer® materials processed using two photon polymerization do not impair cell viability or cell growth. Microneedles were shown to enable more rapid distribution of a model drug (fluorescein-biotin) solution to the deep epidermis and dermis layers of cadaveric porcine skin than topical administration. Ormocer® microneedle arrays penetrated cadaveric porcine adipose tissue without fracture during compression studies.

Conclusions:
Two photon polymerization provides capabilities for scalable fabrication of microscale medical devices as well as patient-specific devices. 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; these devices exhibited appropriate biological, mechanical, and drug delivery properties for clinical use. The results suggest that two photon induced polymerization is able to create medical microdevices with a larger range of sizes, shapes, and materials than conventional polymer, silicon, stainless steel, or titanium microfabrication techniques. It is anticipated that two photon polymerization of medical devices will be translated into clinical use over the coming years.

References:
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2. Ovsianikov A. et al, Int. J. Appl. Ceram. Technol. 2007; 4: 22-29.