Micromachined Biodegradable Microstructures

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ABSTRACT

We present a fabrication approach for the production of micromachined biodegradable microstructures, and illustrate its application in two areas: biodegradable microneedles for transdermal drug delivery, and biodegradable ratcheting surgical ties for blood vessel surgery. We fabricated solid polymer microneedles out of polyglycolide, polylactide and their copolymer using a micromolding technique that created needles with beveled tips. Polymer microneedles were strong enough to be inserted into cadaver skin without breaking. Polymer microneedles impregnated with both low- and high- molecular weight model compounds to simulate drug release were fabricated and inserted into full thickness cadaver skin. Quantitative measurement of model compound release as a function of time was obtained. The fabrication technology was also utilized to produce more mechanically complex biodegradable microstructures: cable ties for surgical ratcheting. These devices were successfully integrated with blood vessel tissue. The change in the mechanical properties of these devices under physiological conditions was investigated and shown to depend on the chemical and physical properties of polymer, implant temperature, and chemical environment.

INTRODUCTION

Micromachined structures made from biodegradable materials have great potential application in areas such as drug delivery, microsurgery, and biological implants. However, since these materials are not commonly used in micromachining applications, fabrication approaches for their realization must be determined in order to understand their limits of application. Micromachined structures have been developed for biomedical applications such as implantable structures (1) and transdermal drug delivery (2,3,4,5). However, previous microstructures have been made of silicon or metal, and in some cases would be incompatible with biological tissue or could leave residue after removal from tissue (5). A fabrication process for polycaprolactone (PCL) microstructures, wherein PCL structures were molded in silicon micromachined molds, was introduced by Liu (6), as a first step towards biocompatible microstructures. Our goals in this study were to develop high aspect ratio structures such as might be necessary for microneedles, and demonstrate more complex mechanical structures. In particular, our goals were to (i) fabricate microstructures out of various biocompatible and biodegradable polymers, (ii) create mechanically intricate microstructures with a three dimensional geometry with high aspect ratio, (iii) exploit the controlled release properties of biodegradable polymer, and (iv) verify their chemical and mechanical properties of microstructure under physiological state in order to understand their limits of biological application. Microneedles were utilized as a research vehicle for exploring high aspect ratio fabrication, and microratchets were utilized as a research vehicle for fabrication of mechanically complex structures. Polyglycolide (PGA), polylactide (PLA) and high molecular weight poly lactide-co-glycolide (PLGA) were used to fabricate microneedles because of their mechanical robustness. Despite their favorable mechanical properties, we were concerned that microneedles fabricated from these polymers might not be strong enough to withstand the force of insertion. We therefore wanted to make needles with sharp, beveled tips to reduce the force required to pierce into skin. Because microneedles with asymmetrically beveled tips have not been made before, we needed to develop a novel fabrication technique to form and mold these structures. The drug or protein was encapsulated in the microneedles for post-insertion release. For long-term implantation of mechanically complex systems, the chemical and mechanical stability of biodegradable microstructures in physiological conditions was considered. Poly L-lactide (PLLA) and polycaprolactone (PCL) were chosen for micro ratcheting surgical ties because they have slower degradation rate and swell less in physiological solutions due to their crystallinity and hydrophobicity.

BIODEGRADABLE MICRONEEDLES

The process for the fabrication of biodegradable microneedles is based on micromolding from

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high-aspect-ratio PDMS masters and is illustrated in Figure 1. It begins by creating a mold from SU-8 epoxy using standard UV-lithographic techniques. SU-8 epoxy was coated onto a silicon wafer and lithographically patterned into cylinders in the shape of the desired needles. The space between the cylinders was filled with a sacrificial polymer (poly lactide-co-glycolide 85/15) and the entire surface was coated with copper by electron beam metal deposition. This copper layer was acid etched to leave a pattern that covered the epoxy cylinders and some of the sacrificial polymer on one side of each cylinder. Reactive ion etching partially removed the uncovered sacrificial layer and asymmetrically etched the tip of the adjacent epoxy cylinders. All remaining sacrificial polymer was removed by organic solvent, leaving an array of epoxy cylinders with asymmetrically beveled tips. This array of needles was coated with polydimethylsiloxane (PDMS) to make an inverse mold. This silicone mold was then used to repeatably mold further polyglycolide (PGA) microneedles (Figure 2). These solid needles have a straight cylindrical shaft that tapers to a beveled tip.

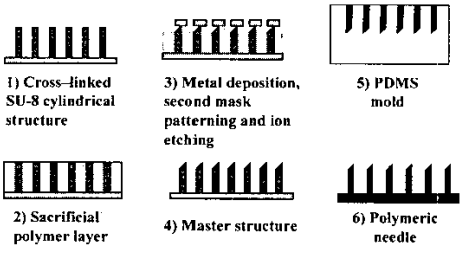

Figure 1: Fabrication sequence of microneedles with beveled tip

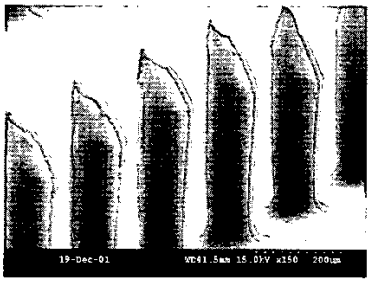

Figure 2 : Scanning electron micrograph images of a portion of an array of beveled PGA microneedles

Biodegradable polymeric microneedles with model compounds for drugs were fabricated using the above process. A low molecular weight model compound, calcein, as well as a high molecular weight compound, bovine serum albumin (BSA) were tested. In the discussion below, the term 'drug' will be used for the calcein measurements and 'protein' will be used for the BSA measurements. Homogenized fine drug or protein particles were dispersed in acetonitrile solution, deposited in the PDMS mold, and dried. This silicone mold with drug or protein particles was then molded with poly-lactide-co-glycolide (PLGA), which yielded the desired PLGA microneedles loaded with drug or protein (Figure 3).

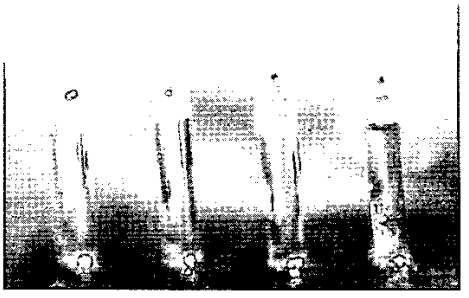

Figure 3 : Optical photomicrographs of a portion of an array of PLGA 50/50 microneedles containing calcein at their tips.

Three tests on biodegradable microneedles were performed. First, insertion into human epidermis was accomplished and qualitatively assessed using electron microscopy. Second, microneedles were loaded with model compounds and release into an aqueous environment was quantitatively assessed. Finally, microneedles were loaded with model compounds and inserted into full thickness cadaver skin, and release into skin as a function of needle depth was assessed using confocal microscopy.

Solid PGA microneedles were inserted into heat-stripped human epidermis to test the ability of biocompatible needles to penetrate without breaking. The epidermis was placed on multiple layers of tissue paper. The polymeric microneedles were placed on the epidermis and pressure was applied. In order to take SEM photomicrographs, the epidermis with needles was fixed in formaldehyde and dried out by a standard ethanol process (7). Figure 4 shows polyglycolide microneedles with beveled tips that were inserted into skin without mechanical failure.

As described above, biodegradable polymeric microneedles can be loaded with drug or protein, which is delivered either by bulk diffusion or upon degradation of the needle. Figure 3 shows an array of poly (lactide-co-glycolide 50/50) microneedles

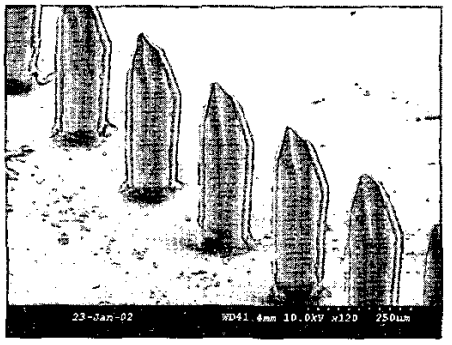

Figure 4 : Scanning electron micrograph images of a portion of an array of beveled polyglycolide microneedles through epidermis

containing calcein at each tip; microneedles with BSA were prepared in a similar fashion. To assess release, microneedles with drug or protein were added to a vial containing phosphate-buffered saline (PBS), pH 7.4. The vials were incubated in a 37°C water bath with stirring. The release medium was sampled from each vial periodically and analyzed to determine the amount of drug or protein released by spectrofluorometry. Each experiment was carried out in triplicate. Figure 5 shows that 93 percent of the calcein was released from the microneedles within four hours in PBS, indicating this formulation of microneedles had fast release and its release pattern depended on calcein bulk diffusion rather than the slower polymer degradation. For BSA, 80 percent of BSA was released from the microneedles in approximately 5 days in PBS, showing its release pattern depended on BSA diffusion and polymer needle surface erosion.

To demonstrate the dissolution and release of drug or protein in actual skin, a confocal microscope study was performed. Polymer microneedles with calcein were applied to full thickness cadaver skin, and the skin/needle assembly was placed in a hydration chamber at a temperature of 4 °C for 8 hours. After 8 hours, the needles were removed and a series of confocal microscope images taken which allowed depth profiling of the released calcein to be performed (Figure 6). Strong images were detected over 200 μm deep into the skin surface.

RATCHETING BIODEGRADABLE MICROSTRUCTURES

Surgical cable ties with microratcheting features were also fabricated using the above process. The devices are not unlike the cable ties used to secure wiring in complex electronic equipment. Three different devices have been fabricated as shown in Figure 7

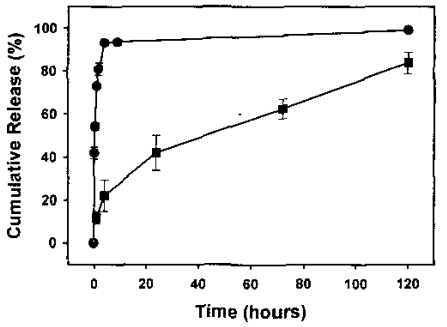

Figure 5: Cumulative release profile for calcein(●) and BSA-fluorescein (■)encapsulated microneedles in PBS

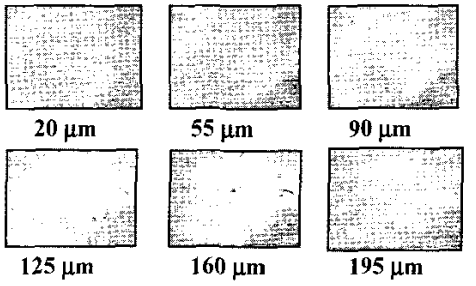

Figure 6: Confocal microscopic images of calcein at different depths in cadaver full thickness skin

and 8. The simplest device is comprised of a 'tail' with asymmetrical projected teeth, and a 'head' consisting of a housing enclosed on two sides and supporting a deflecting beam. By threading the 'tail' through the 'head', the beam deflects to allow each tooth through, but due to the asymmetry of the teeth, reverse motion is not possible. The second device is analogous to a toothed clamp, which can be radially closed around a tube or vessel and the ratcheting teeth of which prevent recoil. The third structure is a semirigid 'barb' that can be linked together with other such barbs to produce a three-dimensional scaffold structure. Figure 9 shows an example of the surgical cable ties in application: a PCL zip tie fastened around a pig carotid blood vessel. Fabrication of these devices proceeds analogously to microneedles, in that silicone molds are used along with PLLA or PCL to form the desired structures. The surface residue was removed with a heated blade prior to release from the mold.

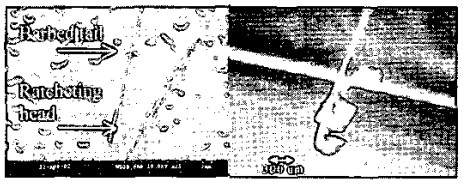

Figure 7: Scanning electron micrograph images of PCL cable tie (left) and photographic images of PCL cable tie around a tweezer (right)

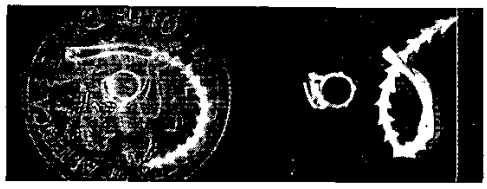

Figure 8: PCL toothed clamp and semi-rigid barb on dime (left) and . radially closed (right)

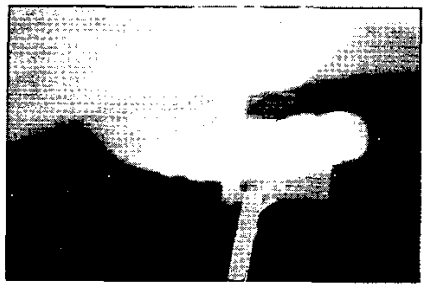

Figure 9: Photographic image of pig carotid blood vessel fastened by PCL zip-tie

To measure the change of mechanical properties of biodegradable cables under physiological conditions, PLLA and PLGA cables with 300μm x 300μm (WxH) cross-section were loaded with various weights in phosphate buffered saline (PBS) at 37°C. The time to ultimate failure under the given load was measured. Figure 10 shows the stress dependence of biodegradable cable failure under physiological condition (37°C, pH 7.4). The PLLA and PLGA cables under physiological condition broke at much lower yield stress than their yield stress under room temperature and air.

CONCLUSION

Using microfabrication and molding techniques, biodegradable polymer microneedles with beveled tips and microratchets with deflecting mechanical structures were created. The polymeric microneedles could contain drug or protein and could penetrate cadaver skin and release drug out into full thickness cadaver skin, demonstrating that biodegradable microneedles can work as a drug reservoir as well as a needle. Ratchet-containing biodegradable cable ties were fabricated and fastened around pig blood vessels. The mechanical properties were considered under room and physiological conditions to understand their long term implantation behavior in the body.

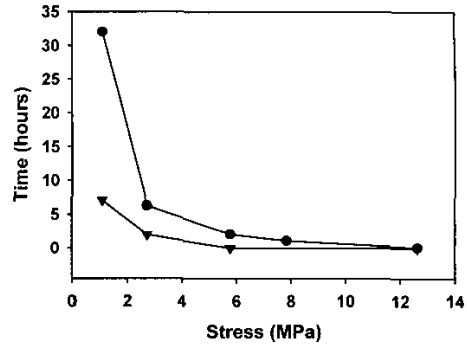

Figure 10: Stress dependence on breaking of PLLA (●) and PLGA (▼)cables in PBS at 37°C

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