A Pure Titanium/Titania Implant for Tunable Zero-Order Drug Delivery

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ABSTRACT SUMMARY

Based on a nanoporous membrane that enables constant release of macromolecules, we have developed a small, complete subcutaneous implant, solely composed of titanium/titania, which is tunable in pore size and implant geometry to accommodate a variety of molecules, potentially improving efficacy and reducing side effects of chronic disease treatments.

INTRODUCTION

Many treatments would benefit from a zero-order release rate, potentially improving efficacy and reducing side effects. Furthermore, a long-term, implantable device may reduce the number of unpleasant injections and improve compliance.

Because their pores are so similar in size to the molecules they deliver, nanoporous membranes have shown the ability to confine molecular diffusion, leading to a constant rate, non-Fickian drug release[1,2]. However, most nanoporous membranes are made of silicon or alumina and attached to a reservoir using an adhesive; none of these materials are commonly used as a tissue-contacting surface in FDA-approved implantable devices.

In contrast, titanium and titanium oxide (titania) have been used for decades with an excellent record of biocompatibility. We previously reported manufacture of an all-titanium/titania membrane, including demonstration of zero-order diffusion *in vitro*, an expected *in vivo* pharmacokinetic profile, and data showing biocompatibility for over a year[2]. In this work, we integrate the membrane into a complete subcutaneous implant, thereby developing new techniques, including tunable pore size optimization, multiple potential assembly techniques, and analysis of loading techniques and capacity.

EXPERIMENTAL METHODS

Following a protocol similar to Paulose, et al[3], vertically aligned titania nanotubes were grown from titanium. To produce a through membrane, a portion of the titanium support structure and the backs of the nanotubes were removed, using an inductively coupled plasma etch[4]. To determine characteristics such as pore size, membranes were imaged using high-resolution scanning electron microscopy (FEI Nova NanoSEM 650). Membranes were attached to reservoirs either temporarily, using a screw-cap prototype with o-rings, or permanently, using a titanium laser weld (DLI Integrations, Lasag SLS C60, Directed Light).

Membranes were loaded into a Cambridge Fiji atomic layer deposition (ALD) machine and received deposition of titania for varying times and with varying cycle parameters to produce different pore sizes.

Two methods of filling were developed: filling by pipette before assembly and filling by a proprietary technique after assembly. Models were generated based on the filling data and on implant geometry, assuming a cylindrical reservoir. Specifically, implant length and diameter were varied to show loading capacity based on formulation concentration. Calculations were done in Microsoft Excel.

RESULTS AND DISCUSSION

A continuous layer of aligned titania nanotubes was grown on titanium and opened to produce a membrane. The titanium support structure was laser-welded to a titanium reservoir with a clean, 400 μm weld bead, at low power. When an un-opened, sham membrane was welded in place using this technique, it produced a testable, hermitic seal, with a helium leak rate of less than 10^{-10} sccm.

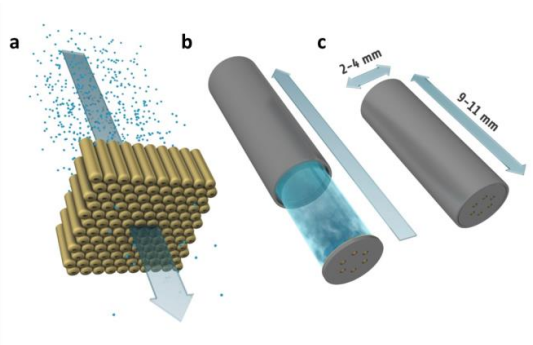

Figure 1. Schematic of nanotube membrane delivery device. a) Vertically aligned nanotube membrane controls flow of molecules. b) Membranes are combined with a reservoir device and loaded. c) Overview of full device.

Atomic layer deposition (ALD) produced pores ranging from 0 nm to 50 nm in diameter (sample images shown in Figure 2). The deposition rate of titania in the ALD runs ranged from 0.62 to 0.68 Å/cycle, and different pore sizes were obtained by varying the ALD cycle number.

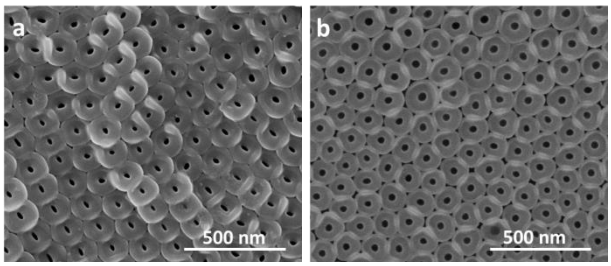

Figure 2. Nanotube pore size optimization. a) 15-25 nm and b) 35-45 nm inner diameter

Complete filling prior to assembly yielded a high percentage of filled reservoir capacity when used in conjunction with the screw-cap prototype, but was not possible when incorporating a laser weld. Filling after assembly was found to load 93.0% +/- 11.9% of reservoir capacity under optimal conditions. Models of loading capacity showed a maximum of 72 mg of drug capacity in a long, narrow device (2 mm diameter – 12 gauge, 4 cm length, 800 mg/ml concentration) and of 340 mg of drug capacity in a long, thick device (4 mm diameter – 7 gauge, 4 cm length, 800 mg/ml concentration – see Fig 3). This corresponds to the drug occupying 71.4% and 84.6%, respectively, of the total device volume.

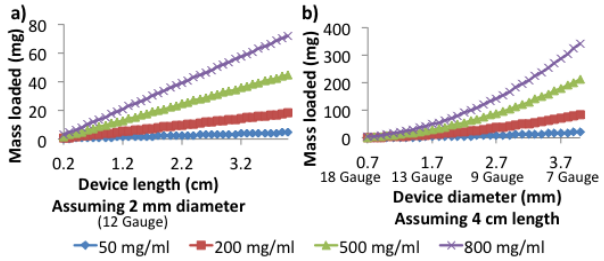

Figure 3. Filling capacity for different devices. a) Thin, 2 mm device, with length varying from 0.2 cm to 4 cm. b) Long, 4 cm device, with diameter varying from 0.7 to 4 mm. On both, concentrations from 50 mg/ml to 800 mg/ml are plotted as different lines (◆ – 50 mg/ml, ■ – 200 mg/ml, ▲ – 500 mg/ml, ✖ – 800 mg/ml).

CONCLUSION

Building on our previous work, which showed that titania nanotube membranes produce zero-order release *in vitro*, generate stable blood concentrations *in vivo*, and remain biocompatible *in vivo* for extended durations[2], we have integrated the membranes into a complete implantable device using solely titanium/titania. This device could be implanted subcutaneously in minutes using a syringe needle in an outpatient setting. Furthermore, we have shown the ability to tune the nanotube pores to a variety of sizes and load a significant mass inside the implant, thereby permitting use with a wide variety of molecules. Because the device allows a high percentage of its volume to be loaded with drug, and we have shown constant release over an extended time irrespective of internal concentration, these nanoporous implants provide an excellent opportunity to reduce side effects and improve efficacy in the treatment of chronic disease.

REFERENCES

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