A Programmable Device for Long-Term Transscleral Drug Delivery

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Statement of Purpose: Chronic retinal diseases such as macular degeneration, diabetic retinopathy and glaucoma cause progressive blindness in millions of patients each year. Several therapeutic compounds have emerged as potential treatments for these diseases, however many challenges remain. One of the principal challenges for treatment of macular degeneration, for instance, is the need for long-term controlled ophthalmic delivery, because these compounds cannot be delivered topically due to transport limitations. Current approaches such as intavitreal injections require repeated treatments at the clinic, are expensive, carry additional risks, and do not provide optimal pharmacokinetics because of limitations in the delivery mechanism. In this work, a programmable and potentially implantable delivery platform for transscleral delivery of compounds is described. The device is designed to be placed directly on the sclera, and is constructed using biocompatible materials and a simple delivery mechanism that can provide virtually constant levels of drug in solid phase to the sclera over periods of a year or more. Early *in vitro* results demonstrate that highly-controlled levels of test compounds are released by the device. Future plans include construction of a fully implantable version for long-term animal studies.

Methods: The drug delivery device described here utilizes a controlled mechanical release mechanism for drug compounds configured in a series of microwells. These microwells, roughly 1.2x0.5x0.13 mm in dimension, are arranged in a two-dimensional array within the surface of a cylindrical drum. Drug is sealed in the wells using a multilayer coating that provides mechanical integrity and is resistant to moisture penetration. The drug cylinder sits within a casing, adjacent to a penetrator drum with a series of needles projecting from its surface. A simple oscillator circuit powered by a miniaturized battery causes the drug cylinder and the penetrator cylinder to rotate against one another, opening drug wells to enable release of drug from each of the wells in a sequential manner (Fig. 2.) Drug is then released to the region against the scleral surface, and reaches the macula through a transscleral diffusion process described earlier [1]. A typical protocol involves penetration of a microwell every 2 – 4 days for periods of one year or more. Initial studies entail construction of an *in vitro* prototype of the concept, in which the rotational mechanism is powered by an external supply and is controlled by an external circuit. A test compound, rhodamine-labeled dextran (40 kD) was loaded into the wells and then released into a test tube. Test compound levels in solution are measured using uv-visible absorbance spectrophotometry.

Results / Discussion: Initial results of the *in vitro* evaluation of this device are very encouraging, with highly controlled levels of the test compound measured in solution. Drug compound is repeatably and completely released from the wells via mixing with the liquid within the test tube. The device with the cover removed is shown in Figure 1. In Figure 2, a fluorescent image of a section of the drum surface shows an array of microwells, loaded with the rhodamine-labeled dextran.

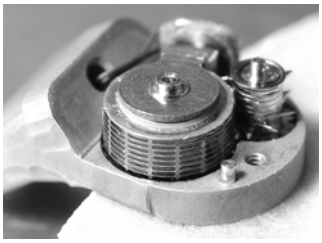

Figure 1

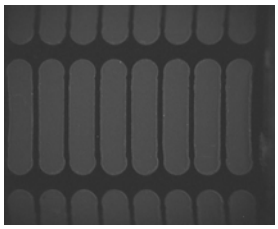

Figure 2

In an initial test, wells were opened sequentially, in an accelerated fashion, to determine the concentration of the rhodamine-labeled dextran in a beaker as a function of time. Concentration vs. time for two experiments is shown in Fig. 3. The two sets of data each represent the concentration profile after the opening of an individual well. The data shows good agreement with the concentration predicted by complete release of a single well, and good repeatability across the two data sets. The uniformity of compound loading in the individual wells was also measured, and was found to be within +/- 2% is achieved across the 120 microwells.

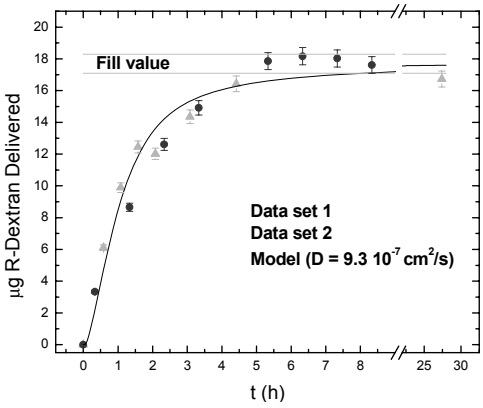

Figure 3.

Conclusions: In this work a novel ophthalmic drug delivery device is described, and prototype testing in vitro with a fluorescently labeled test compound is presented. Uniform filling of the microwells is demonstrated, and concentrations in a test tube are shown to reach predicted equilibrium levels. Next steps include the construction of a fully implantable version for animal studies.

References:

1. Ambati J, Canakis CS, Miller JW, Gragoudas ES, Edwards A, Weissgold DJ, Kim I, Delori FC, Adamis AP., *Invest Ophthalmol Vis Sci.* 2000; 41(5):1181-1185