

Microneedles for Ocular Drug Delivery

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Statement of Purpose: Targeted drug delivery into the eye is a challenging task because of a variety of barriers that prevent safe and effective delivery. Topical application to the eye is hindered by low residence time resulting in poor diffusion of drug into intraocular tissues. Intravitreal injection can deliver drugs to the retina effectively but is invasive and carries risk of infection. In this study, we aim to assess the capability of a novel drug delivery device, the microneedle, to deliver drugs to the eye in a minimally invasive yet effective way. We examine whether microneedles can deliver to the posterior segment (i.e., intrascleral and suprachoroidal) and the anterior segment (i.e., intracorneal). We assess whether microneedles can deliver a fluid and suspension of nanoparticles or microparticles targeted to these regions in a minimally invasive way.

Methods: To assess hollow microneedles for injection within the sclera (intrascleral), a hollow glass microneedle was inserted into human cadaver sclera for infusion of a sulforhodamine solution, poly-lactic acid nanoparticle and microparticle suspension. Hollow glass microneedles were also used to infuse carboxylate-modified polystyrene nanoparticle and microparticle suspensions into the suprachoroidal space by inserting across the sclera. These experiments were performed on whole rabbit, and pig eyes *in vitro*. Delivery was verified visually, as well as using fluorescence microscopy using whole eyes and cryosection histology. To assess microneedles for delivery to the anterior of the eye, solid stainless steel microneedles coated with sodium fluorescein were inserted into the rabbit cornea *in vivo*. The metal needles were coated using a poly-vinyl-pyrrolidone (PVP) based aqueous coating solution. The needle was then removed and fluorescein concentrations in the anterior segment were measured for up to 24 h in real time using a fluorometer. Similar experiments were repeated using microneedles coated with pilocarpine. The rabbit pupil size was monitored over time to determine effectiveness of pilocarpine delivery.

Results: Hollow microneedles were used to assess delivery into the posterior segment of the eye. They were shown to insert into but not penetrate across human cadaver sclera and inject tens of microliters of model drug solutions and nanoparticle suspensions within the sclera. Successful delivery of micron-sized particles into the sclera was improved by breaking down tightly packed collagen or GAG fibers using either collagenase or hyaluronidase. Hollow microneedles were also shown to deliver nanoparticle and microparticle suspensions into the suprachoroidal space of rabbit and pig eyes. Particle diameters used include 20 nm, 100 nm, 500 nm, and 1

μm . Volumes of delivery ranged from 15-30 μL in the space using a single microneedle; volumes delivered to rabbit eyes were lower compared to pig eyes. Pressures required for delivery ranged from 150 kPa to 300 kPa with a small dependence on particle size. Insertion depth for suprachoroidal delivery was 500-700 μm in rabbit and 700-1000 μm in pig. Solid metal microneedles were used to assess delivery into the anterior of the eye. They were shown to insert into rabbit cornea *in vivo*. Sodium fluorescein was coated on the surface and after insertion completely dissolved off the needles within 30 sec, which resulted in fluorescein concentrations in the anterior chamber 70 times greater than those achieved by topical delivery of fluorescein without microneedles. Similarly, microneedle delivery of pilocarpine caused rapid and extensive pupil constriction. There was no inflammatory response or other adverse effects observed when using these microneedles.

Conclusions: Microneedles have shown for the first time to deliver within the sclera, suprachoroidal space *in vitro* and into the anterior portion of the eye *in vivo*.

Microneedles, because of their size, may provide a minimally invasive way to deliver drugs and particle suspensions targeted to a specific region in the eye. The capability to deliver particle suspensions opens the way to provide for controlled drug delivery to the eye as they can be made of a variety of materials and sizes. This can help reduce dosing frequency and also allowing for better therapeutic control. This novel technology can help reduce the complications associated with current delivery methods such as intraocular injection, systemic administration and topical delivery.

References:

Jiang, J., et al., Coated microneedles for drug delivery to the eye. *Investigative Ophthalmology & Visual Science*, 2007. 48(9): p. 4038-4043