Precisely Engineered Biodegradable Intraocular Implants for the Sustained Release of Dexamethasone

Andres Garcia, Janet Tully, Benjamin Maynor, Benjamin Yerxa.

Liquidia Technologies, P.O. Box 110085, RTP, NC 27709

Corresponding Author: Andres Garcia, andres.garcia@liquidia.com, (919) 328-4388

Purpose

The ability to fabricate biodegradable intraocular implants with uniform size, shape and dose for the sustained delivery of actives in multiple regions of the eye has proven elusive with current technologies. The acceptance of intraocular implants for the localized treatment of multiple back-of-the-eye conditions has paved the way for the development of a new generation of smaller intraocular implants in the anatomically and clinically desirable, yet "hard-to-manufacture" size range of 100μm to 1,000μm. The ability to reproducibly fabricate implants in this size range opens up a window of opportunities for the injection and localization of implants against multiple target tissues of the inner eye where greater spatial constraints may exist. We have previously described a novel particle manufacturing technology, Particle Replication in Non-Wetting Templates (PRINT®), for the production of monodisperse particles across multiple areas of drug delivery (1), as outlined in Figure 1. Given the PRINT methodology, we report the ability to precisely fabricate 200μm x 200μm x 1,000μm biodegradable implants for the sustained delivery of actives in the eye.

Methods

Using the PRINT technology four implant formulations comprised of a blend of 20% w/w dexamethasone (DXM) and 80% of a biodegradable polymer (with varying degrees of molecular weights and lactide-glycolide ratios) were prepared:

- **Formulation 1**: dexamethasone / Poly(D-L-lactide)
- **Formulation 2**: dexamethasone / Poly(D-L-lactide)
- **Formulation 3**: dexamethasone / Poly(D-L-lactide-co-glycolide)
- **Formulation 4**: dexamethasone / Poly(D-lactide-co-glycolide)

Physicochemical characterization of the implants was performed and dexamethasone release in vitro was evaluated:

- **Physical morphology**: implants were analyzed by scanning electron microscopy. 
- **Overall mass uniformity**: mass of individual PRINT implants (n=15) was measured using Mettler MT3 microbalance for all formulations.
- **Dexamethasone content uniformity**: Dexamethasone content of individual PRINT implants at t=0 (n=15) was measured using a RP-HPLC method and Phenomenex Luna Phenyl-Hexyl 3μm particle size, 4.6 x 100 mm analytical column. Mobile phase consisted of a gradient of 0.1% TFA in purified water and 0.1% TFA in acetonitrile over 12 minutes at 1 mL/min. UV absorbance of dexamethasone was measured at 240 nm.
- **In vitro release of dexamethasone from the implants**: The release profiles of individual PRINT implants (n=20) were monitored at sink conditions for 141 days. Individual PRINT implants were incubated in 500μL of 1X PBS at 37°C (total possible dexamethasone concentration in release media = 20μg/mL). Supernatant of each was sampled at 1, 3, 7, and 14 days, and at 4 week intervals thereafter, to measure cumulative dexamethasone released from implants.

- **Initial in-vivo implant injections**: PRINT implants were placed in a 25G needle on a syringe profiled with viscoelastic solution (Viscofluff sodium hyaluronate – sodium chondroitin sulfate). Intravitreal injection sites were performed on anesthetized New Zealand white rabbits under operative microscope. Approximately 50μL of Viscofluff were injected along with the implant. Fundus was observed using the slit lamp 15min after the injection, on day 2, 7 and 14. Implant was retrieved from vitreous on day 21. Similarly, subconjunctival and intracameral injections were performed and implants were evaluated over time.

Results

![Figure 2. Scanning electron micrographs of four different implant formulations consisting of a blend of dexamethasone and a biodegradable polymer. Implant size for all formulations: 200μm x 200μm x 1,000μm.](image)

**Table 1. Summary of implant mass uniformity, measured dexamethasone loading in implant formulations and % dexamethasone released from implants in-vitro after 141 days in 1X PBS at 37°C.**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Measured PRINT implant mass at t = 0 (μg)</th>
<th>Measured DXM mass in individual PRINT implants by HPLC at t = 0 (μg)</th>
<th>Measured % DXM loading in PRINT implants at t = 0 (API mass/implant mass)</th>
<th>141 day in-vitro evaluation of % DXM released from PRINT implants at t = 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>FORMULATION 1</td>
<td>52 μg</td>
<td>1 μg</td>
<td>10 μg</td>
<td>1 μg</td>
</tr>
<tr>
<td>FORMULATION 2</td>
<td>53 μg</td>
<td>1 μg</td>
<td>9 μg</td>
<td>1 μg</td>
</tr>
<tr>
<td>FORMULATION 3</td>
<td>54 μg</td>
<td>1 μg</td>
<td>9 μg</td>
<td>1 μg</td>
</tr>
<tr>
<td>FORMULATION 4</td>
<td>51 μg</td>
<td>1 μg</td>
<td>9 μg</td>
<td>1 μg</td>
</tr>
</tbody>
</table>

Conclusions

The PRINT technology uniquely allows for the fabrication of intraocular implants with uniform size, shape and dose. We demonstrated the ability to fabricate dexamethasone intraocular implants in the desirable size range of 100μm to 1,000μm for sustained release applications where anatomical constraints may call for uniquely engineered implants. PRINT implants are well tolerated in vivo and offer a unique, new paradigm for the sustained delivery of actives in the eye.

Commercial Relationships

Andres Garcia, Janet Tully, Benjamin Maynor and Benjamin Yerxa are all employees (E) of, and have personal financial interest (I) in, Liquidia Technologies.

References: