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DEXAMETHASONE INTRAVITREAL IMPLANTS: MANUFACTURE, CHARACTERIZATION, AND ELUCIDATION OF DRUG RELEASE MECHANISMS

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PURPOSE

Ozurdex (dexamethasone intravitreal implant, 0.7 mg) is an FDA–approved, long-acting implant formulated to deliver the corticosteroid dexamethasone to the posterior segment of the eye for the treatment of macular edema and noninfectious uveitis. Sustained drug release is achieved by embedding the drug in a biodegradable poly(lactic-co-glycolic acid) (PLGA) matrix that gradually releases the drug directly into the vitreous over the course of 3–6 months.[1] The rod-shaped, six-millimeter-long implant is produced using a continuous hot-melt extrusion process in which the drug and polymer are mixed at temperatures above the glass transition temperature (T_g) of the polymer.

Study objectives:

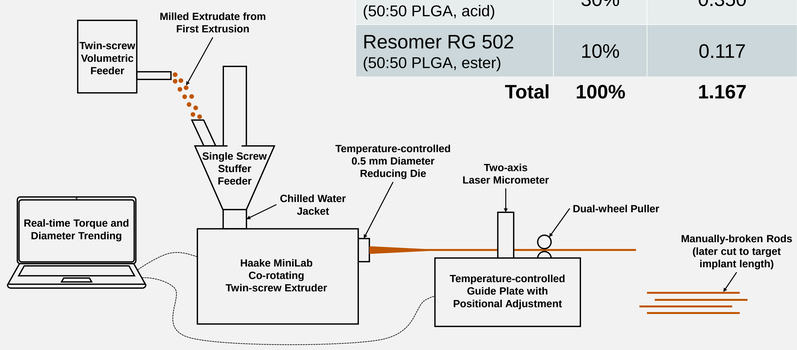
- Perform detailed physicochemical and structural characterization of Ozurdex
- Reverse-engineer the Ozurdex implant
- Elucidate the mechanisms of controlled drug release using the reverse-engineered implant

METHOD(S)

Dexamethasone intravitreal implants were prepared using a two-step hot melt extrusion process. The first extrusion is used to densify the pre-extrusion blend into a free-flowing material that can be fed consistently during the second extrusion and implant shaping process. In the second extrusion, a single-screw stuffer feeder in tandem with a twin-screw volumetric feeder was used to feed a Haake MiniLab twin-screw extruder set to 105°C fitted with co-rotating screws set to 125 rpm. At the extruder discharge port, a heated die (0.5 mm diameter) was used to change the extrusion melt profile from rectangular to cylindrical in a reducing channel. The diameter of the cylindrical melt was reduced to the target value using a dual-wheel puller with manual speed control. The implant diameter was measured with a two-axis laser micrometer. Real-time process monitoring and trending of extruder torque and implant diameter was implemented using MATLAB.

Composition of the dexamethasone intravitreal implants prepared in this study.

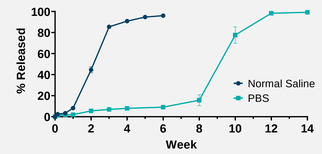
Material	Amount (% w/w)	Mass/implant (mg)
Dexamethasone (Form B, micronized)	60%	0.700
Resomer RG 502 H (50:50 PLGA, acid)	30%	0.350
Resomer RG 502 (50:50 PLGA, ester)	10%	0.117
Total	**100%**	**1.167**



Second step of the two-step melt extrusion process used to prepare the dexamethasone intravitreal implants.

CONCLUSION(S)

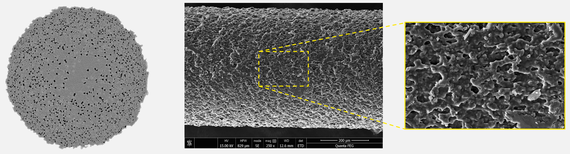
- Ozurdex exists as a two-phase system of dexamethasone crystals uniformly embedded in a PLGA matrix due to limited intermolecular interaction between the drug and the polymer.
- Reverse-engineered implants that are compositionally and structurally equivalent to Ozurdex were prepared using a two-step hot-melt extrusion and shaping process.
  - Control of implant diameter, surface roughness, and internal porosity during the manufacturing process are required to maintain dose uniformity.
- The reverse-engineered implant exhibits a triphasic drug release profile very similar to that of Ozurdex.[2, 3]
  - **Phase 1:** Limited burst release due to inaccessibility of dexamethasone crystals coated in PLGA on implant surface
  - **Phase 2:** Lag phase with very little drug release while PLGA hydrolysis is actively occurring
  - **Phase 3:** Release to completion dictated by erosion/diffusion of PLGA oligomers



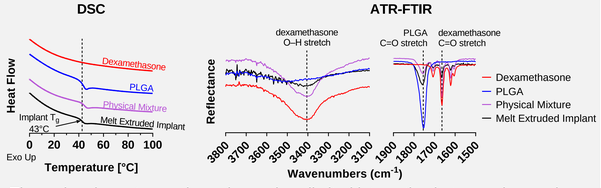
In vitro dissolution comparison of dexamethasone intravitreal implants in normal saline and phosphate-buffered saline (PBS) at 37°C (N=3, mean ± SD). The buffering capacity of PBS reduces the auto-catalytic hydrolysis of PLGA and dramatically extends the second phase of release.

RESULT(S)

Characterization of Ozurdex and the PLGA–dexamethasone Interaction

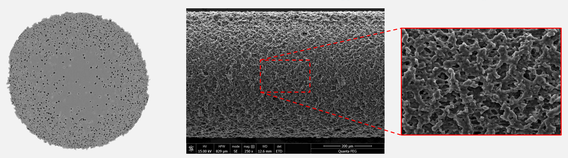


MicroCT cross-section and scanning electron microscope (SEM) profiles (250x, 1000x) of Ozurdex. The implant exhibits an irregular surface with few free crystals of dexamethasone and an internal porosity of 6% due to many discrete voids approximately 3 µm in diameter.

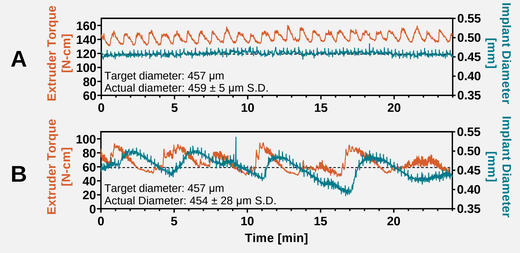


Thermal and spectroscopic analyses show limited interaction between drug and polymer. Differential scanning calorimetry (DSC) shows no depression in the T_g of PLGA after melt extrusion. Fourier-transform infrared spectroscopy (FTIR) demonstrates the lack of hydrogen bonding interactions between dexamethasone and PLGA. Ozurdex exists as a two-phase system of dexamethasone crystals embedded within a PLGA matrix.

Manufacture of Reverse-Engineered Implants

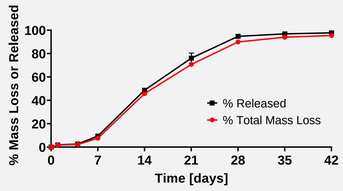


MicroCT cross-section and SEM profiles (250x, 1000x) of the reverse-engineered implant. The implant exhibits structural characteristics very similar to Ozurdex, including (a) an irregular surface with few free crystals of dexamethasone, (b) a consistent diameter, and (c) an internal porosity of 6% due to many discrete voids approximately 3 µm in diameter.



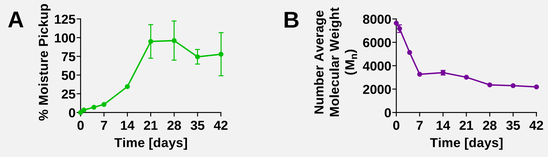
Example of good feeding control (A) and poor feeding control (B) during the implant manufacturing process. Under good feeding control, small, predictable fluctuations in extruder torque enable accurate control of implant diameter. Under poor feeding control, feeding variability generates large, unpredictable variations in process torque and corresponding variability in implant diameter.

Mechanisms of Controlled Drug Release



$$\%\ Total\ Mass\ Loss\ (t) = \frac{m_0 - m(t)_{lyophilized}}{m_0}$$

In vitro dissolution of the reverse-engineered implant in normal saline at 37°C (N=6, mean ± SD), overlayed with total mass loss from the implant. Total mass loss trends closely with drug release, suggesting an erosion-based mechanism. The implant exhibits a triphasic release profile with 1) a limited burst release, 2) a one-week lag phase, and 3) a release to completion.



$$\%\ Moisture\ Pickup\ (t) = \frac{m(t)_{wet} - m(t)_{lyophilized}}{m(t)_{lyophilized}}$$

Implant moisture pickup (A) and change in PLGA molecular weight (B) during in vitro dissolution testing in normal saline at 37°C (N=6, mean ± SD). Despite limited drug release in the first week (< 10%), implant water uptake begins immediately and drives significant hydrolysis of the PLGA.

FUNDING AND REFERENCES

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