Manufacture and process control of dexamethasone intravitreal implants produced by hot melt extrusion

Poster # 315

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Introduction

Ozurdex® (dexamethasone intravitreal implant) is a long-acting, biodegradable implant containing dexamethasone and poly(lactic-co-glycolic acid) (PLGA) indicated for treatment of macular edema and noninfectious uveitis (1) (**Figure 1**). The rod-shaped implant is administered directly to the posterior segment of the eye via a 22-gauge thin wall needle (2). Several unique manufacturing challenges exist to produce dexamethasone intravitreal implants with appropriate internal and external morphology. Precise diameter control of the implant is required to fit within the applicator needle barrel, and control of implant internal porosity is necessary to ensure dose uniformity based on geometric constraints (3). This study explores the impact of process parameters and die design on dexamethasone intravitreal implant morphology during the melt extrusion process.

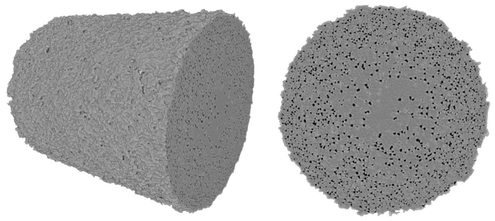

Figure 1. MicroCT reconstruction of a dexamethasone intravitreal implant

Discussion

A two-step extrusion process was developed for manufacture of dexamethasone intravitreal implants. The first extrusion serves primarily to densify the blended components into rods that are subsequently milled into free-flowing granules to enable consistent feeding during the second extrusion (**Figure 2**).

When feeding the extruder with a single-screw stuffer feeder, real-time process monitoring revealed high variability in extruder torque that resulted in similar perturbations in implant diameter on a 1-2 minute time lag (**Figure 4,A**). This phase-shifted response in implant diameter stemming from torque fluctuations highlights the importance of consistent feeding to produce dexamethasone intravitreal implants of appropriate dimensions. The addition of a volumetric feeder to meter the flow of milled extrudate into the stuffer feeder at 8-10 g/hr reduced torque variability and dramatically improved diameter control (**Figure 4,B**).

A tracer die was used to visualize and quantify the mean residence time of the implant extrusion process by monitoring color change over time using a scientific camera (4). At a feed rate of 10 g/hr, the mean residence time was determined to be 33 minutes (**Figure 5**). This long residence time is expected to result in intimate mixing between crystalline dexamethasone and PLGA, producing an implant with a uniform cross-section.

Changes to the diameter and land length of the reducing die at the extruder exit were found to significantly alter extruder torque and implant internal porosity (**Figure 6**). It is hypothesized that the more restrictive dies with a smaller diameter and longer land length contribute to greater holdup in the extruder barrel which translates to increased process torque. Higher process torque trends with a decrease in implant porosity, perhaps due to an extended residence time in the extruder barrel driving out the bubbles contained within the melt. SEM images (**Figure 7**) show how changes to the die design can alter implant porosity, pore size, and distribution. A linear, empirical model with die cross-sectional area (i.e., diameter) and land length was fit to implant porosity with a strong correlation (**Figure 8**).

Materials and Methods

Dexamethasone intravitreal implants were prepared with the following composition: 60% micronized dexamethasone, 30% Resomer RG 502 H (50:50 PLGA, acid-terminated), and 10% Resomer RG 502 (50:50 PLGA, ester-terminated). A single-screw stuffer feeder in tandem with a twin-screw volumetric feeder was used to feed a Haake MiniLab twin-screw extruder at 105°C fitted with co-rotating screws rotating at 125 rpm (**Figure 2**). A heated die with a 0.48 mm or 0.55 mm diameter was used to change the extrusion melt profile from rectangular to cylindrical in a reducing channel (**Figure 3**). The cylindrical melt was reduced to the target diameter via a dual-wheel puller with manual speed control and the 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. Implant density was determined by careful measurement of implant diameter, length, and mass. Porosity was determined using the true density of the implant components determined by helium pycnometry.

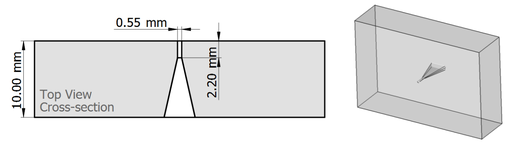

Figure 3. Reducing die design for melt extrusion, 0.55 mm diameter, 2.20 mm land length (4:1 L:D).

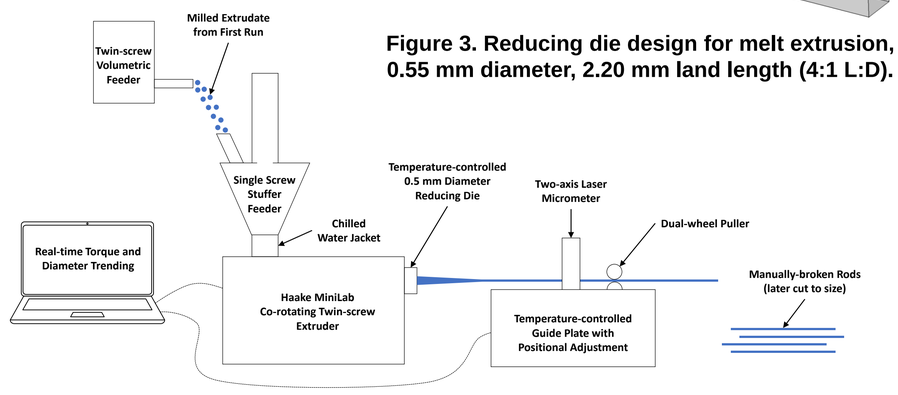

Figure 2. Illustration of process used to produce dexamethasone intravitreal implants.

Results

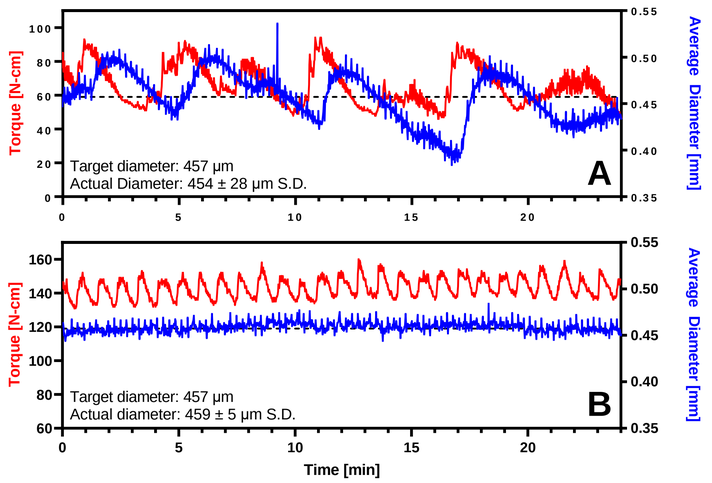

Figure 4. Trending of extruder torque and implant diameter before (A) and after (B) feeding optimization. Feeding variability contributes to extruder torque variation and subsequent variability in implant diameter.

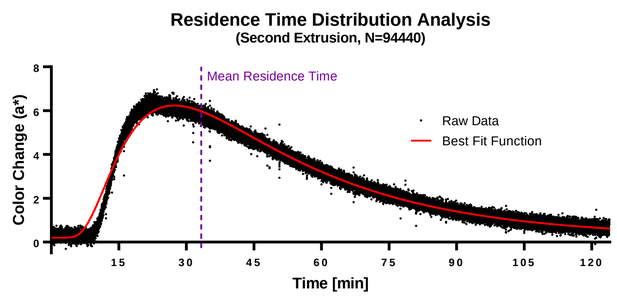

Figure 5. Residence time distribution analysis of the melt extrusion process used to produce dexamethasone intravitreal implants. Mean residence time = 33 minutes.

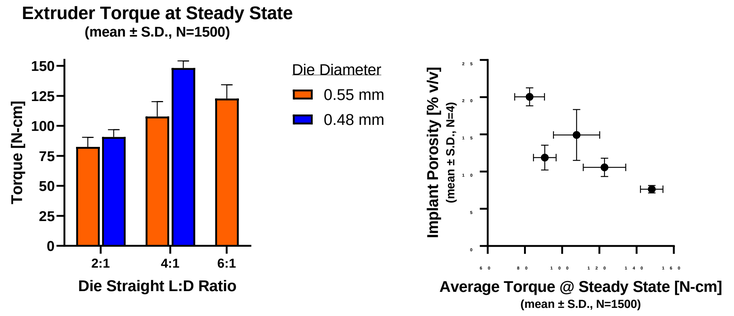

Figure 6. Restrictive dies contribute to higher process torque and reduced implant porosity.

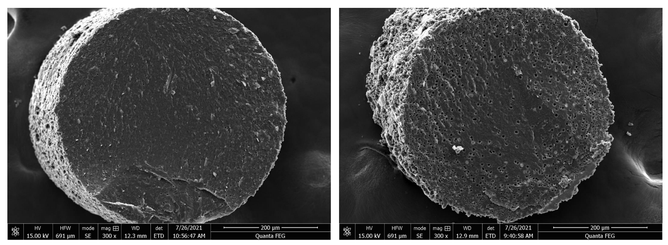

Figure 7. Dexamethasone intravitreal implants of different porosity. Left: 8%, from 0.48 mm, 4:1 die. Right: 20%, from 0.55 mm, 2:1 die.

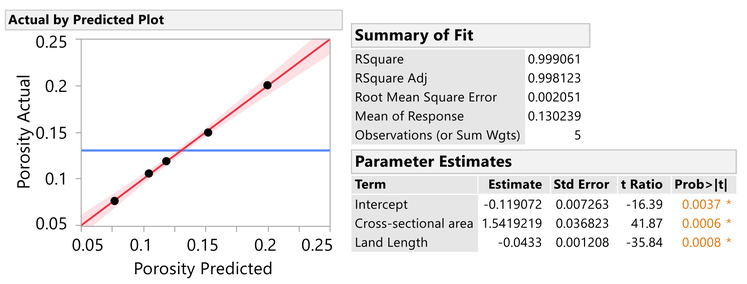

Figure 8. Empirical model of die design parameters and dexamethasone intravitreal implant internal porosity.

Conclusions

1. Maintaining feeding accuracy during melt extrusion of dexamethasone intravitreal implants is critical for accurate dimension control.
2. Long extruder residence time (33 minutes) contributes to intimate mixing of dexamethasone and PLGA, resulting in a uniform dispersion of dexamethasone in a PLGA matrix.
3. Implant internal porosity can be altered by changing extruder die geometry: diameter and land length.

References

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Acknowledgements and Contact Info

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