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ROLE OF PLGA VARIABILITY IN CONTROLLED DRUG RELEASE FROM DEXAMETHASONE INTRAVITREAL IMPLANTS

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PURPOSE

Generic formulations of poly(lactide-*co*-glycolide) (PLGA)–based long acting injectables are largely absent in the market, despite many of the innovator drug products extending well beyond their patent protection. The inherent complexity of the copolymer renders the development, manufacture, and scale-up of generic equivalent formulations very challenging. In one example, differences in the ordering of the lactic acid and glycolic acid monomer units on the polymer chain (blockiness) have been shown to impact PLGA degradation and drug release kinetics.[1] This work used Ozurdex (dexamethasone intravitreal implant)[2] as a model system to evaluate the impact of small changes in PLGA physicochemical properties on drug release kinetics in vitro.

OBJECTIVE

Compare the in vitro release profiles of four structurally equivalent dexamethasone intravitreal implants prepared with four different lots of acid-terminated PLGA with the following composition:

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

Composition of the dexamethasone intravitreal implants prepared in this study. The source of acid-terminated PLGA was varied. A single lot of dexamethasone and a single lot of ester-terminated PLGA was used.

METHOD

Dexamethasone intravitreal implants were prepared using a Haake MiniLab twin-screw extruder in a two-step extrusion process.[3] The first extrusion was used to densify the pre-extrusion blend into a free-flowing material that enabled accurate dimensional control during the second extrusion. Implants were shaped to a target diameter of 457 µm and cut to 6 mm in length. Extruder conditions (second extrusion): 105 °C barrel temperature; 75 rpm screw speed; 8.5 g/h feed rate.

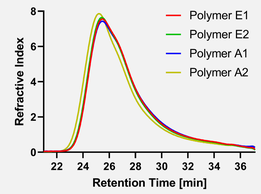
RESULTS

Subtle differences in physiochemical properties of the four acid-terminated PLGAs

Two lots of Evonik Resomer RG 502 H PLGA (Polymer E1, Polymer E2) and two custom synthesis Akina Inc. 50:50 acid-terminated PLGAs with similar molecular weight (Polymer A1 and Polymer A2) were used in this work. The polymerization reaction conditions of the two Akina PLGAs were deliberately altered to produce polymers of different blockiness. Polymer A1 had a higher acid number than the other three acid-terminated polymers.

Polymer	M_w (g/mol) (N=3)	T_g (°C) (N=3)	Moisture Content (% w/w) (N=3)	L/G Ratio	Residual Monomer (% w/w)	G Block Length	Acid Number (mg NaOH/g) (N=5)
E1 (●)	19283 (324)	44.7 (0.6)	0.32 (0.01)	50/50	0.13	2.53	8.3 (0.2)
E2 (■)	19875 (312)	44.7 (0.8)	0.36 (0.02)	51/49	0.10	2.45	8.0 (0.1)
A1 (▲)	19387 (206)	42.6 (0.2)	0.29 (0.01)	52/48	0.26	2.54	9.7 (0.2)
A2 (▼)	22487 (215)	43.6 (0.4)	0.32 (0.01)	52/48	0.31	2.25	8.6 (0.1)
Ester	24076 (170)	43.3 (0.3)	0.25 (0.01)	51/49	0.08	2.56	N/A

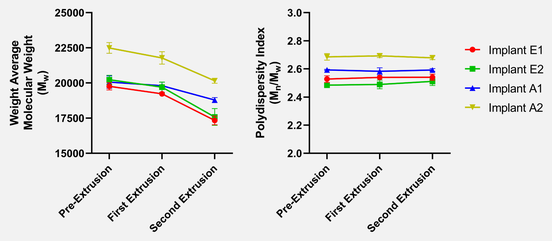
Properties of the PLGAs evaluated in this study, mean (S.D.). Outliers are highlighted in orange. The symbol and color convention presented in the first column is used throughout this work.



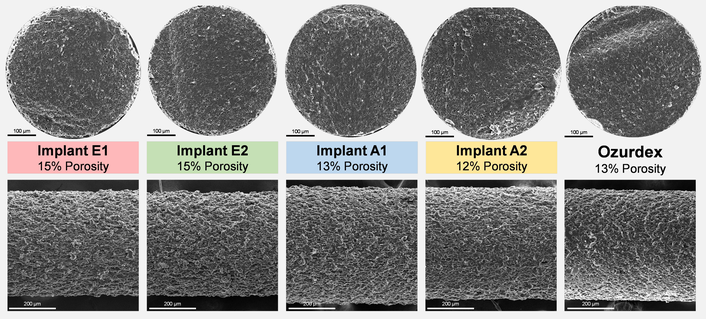
Area-normalized mean chromatograms (N=3) from GPC analysis of the four acid-terminated PLGAs illustrating their similar molecular weight distributions.

Implants structurally equivalent to one another

Polymer source had no impact to total implant porosity or internal pore size/distribution. All implants had an average diameter of 458 µm. All samples showed a ~10% reduction in PLGA molecular weight after the second melt extrusion process.



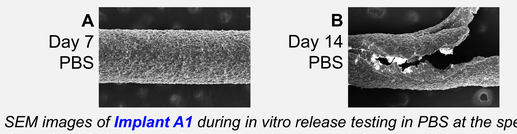
Average PLGA molecular weight and polydispersity index throughout the two-step extrusion process used to produce the implants. Mean ± S.D., N=3.



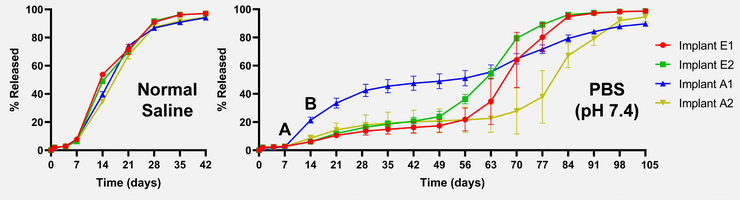
Scanning electron microscope (SEM) images of Ozurdex and the four dexamethasone intravitreal implants produced in this study. Top row: cross-sections revealing internal porosity. Bottom row: profiles revealing surface morphology.

In vitro release testing medium affects sensitivity to subtle differences in PLGA properties

No difference in release profiles was observed in normal saline. In PBS, the duration of release was extended approximately 3-fold and a unique release profile was observed for each implant.



*SEM images of **Implant A1** during in vitro release testing in PBS at the specified timepoints. Only Implant A1 showed this structural change, which resulted in more drug release on Days 14–28 compared to the other implants.*



In vitro release profiles of the four implants in unbuffered normal saline and phosphate-buffered saline (PBS). Mean ± S.D., N=6.

CONCLUSIONS

- The four acid-terminated PLGAs used to prepare the dexamethasone intravitreal implants in this study were similar in molecular weight, T_g, moisture content, and lactide/glycolide ratio.
- Subtle differences in residual monomer content, PLGA blockiness, and carboxylic acid end group content (acid number) of the polymers were observed.
- The two-step, hot-melt extrusion process used to prepare the implants was not sensitive to small differences in PLGA properties. The four implants were structurally equivalent to one another and the Ozurdex reference product.
- In vitro release testing in PBS was found to be dramatically more sensitive to the subtle differences in PLGA properties compared to normal saline.
- Further studies are needed to clarify which in vitro release testing method is more physiologically relevant to discern meaningful differences in the formulations. Our future work includes plans to test these implants in rabbit eye.

FUNDING AND REFERENCES

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