14 JULY 2022

TEXAS
The University of Texas at Austin

DEXAMETHASONE INTRAVITREAL IMPLANTS: CHARACTERIZATION AND ELUCIDATION OF DRUG RELEASE MECHANISMS

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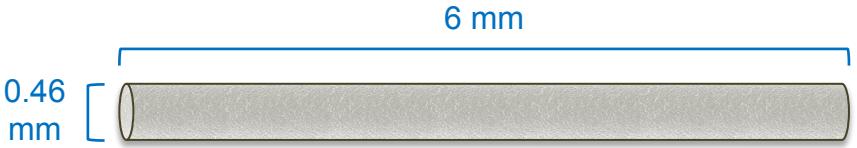
About Ozurdex (dexamethasone intravitreal implant)

- Rod-shaped, solid implant produced by a continuous hot melt extrusion process
- Biodegradable poly(D,L-lactic-*co*-glycolic acid) (PLGA) matrix
- Delivered via a proprietary injector housing the implant within hypodermic needle

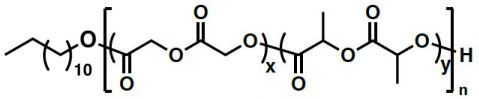
Drug/Dose	Manufacturer	Indication	Duration of Release
Dexamethasone, 700 µg	Allergan (AbbVie)	non-infectious uveitis diabetic macular edema retinal vein occlusion	3-6 months



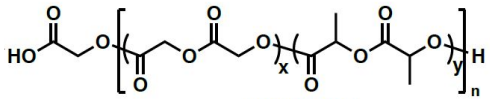
- 60% drug loading
- Matrix contains two grades of 50:50 PLGA

Glycolide Lactide

Ester-terminated
"hydrophobic PLGA"



Acid-terminated
"hydrophilic PLGA"

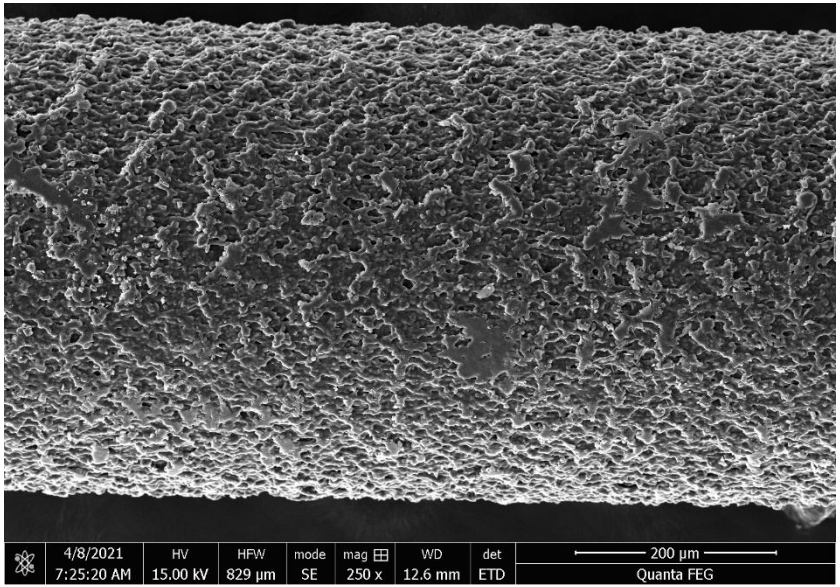


OZURDEX® Prescribing Information. 2020. Available from: https://www.rxabbvie.com/pdf/ozurdex_pi.pdf.
CHMP Assessment report - Ozurdex. London, UK; 2010.

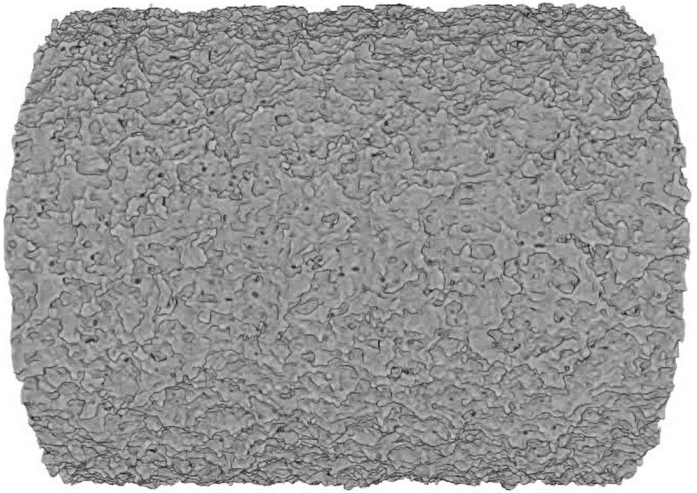
Structural analysis of Ozurdex

SEM and MicroCT reveal irregular surface and 6% internal porosity

SEM profile



MicroCT profile



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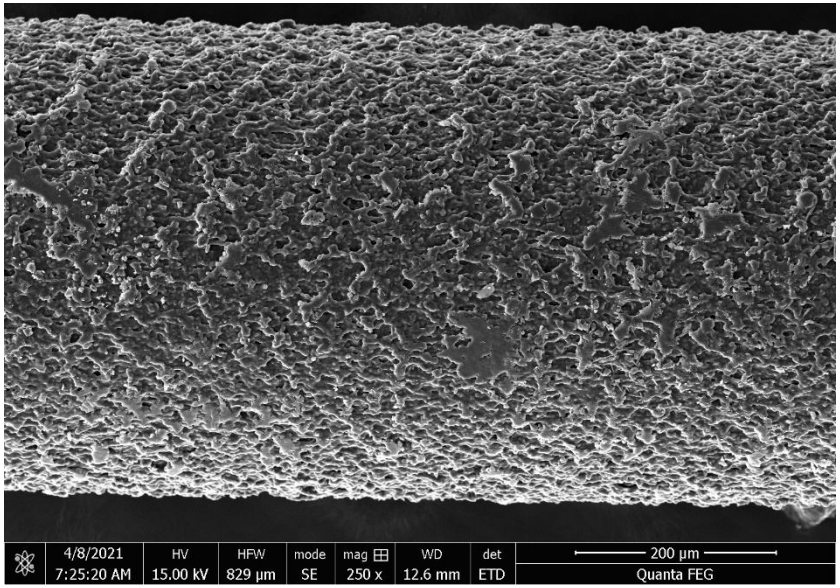

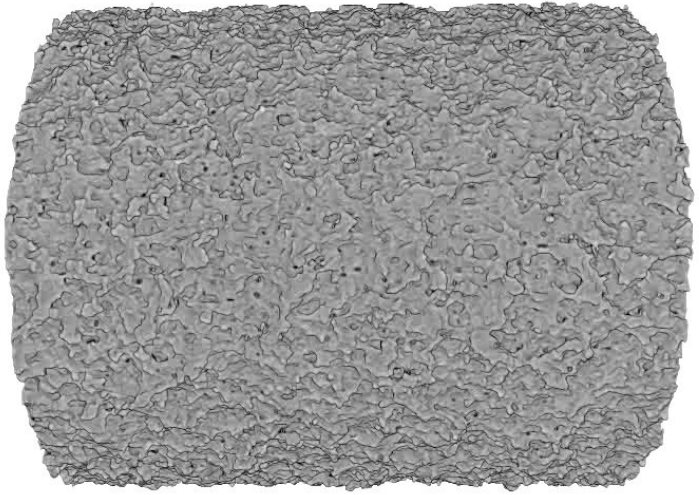

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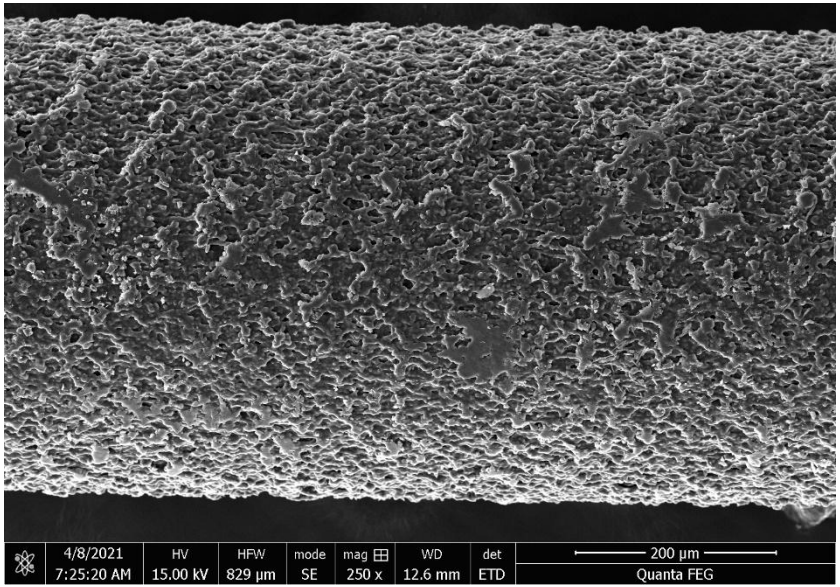
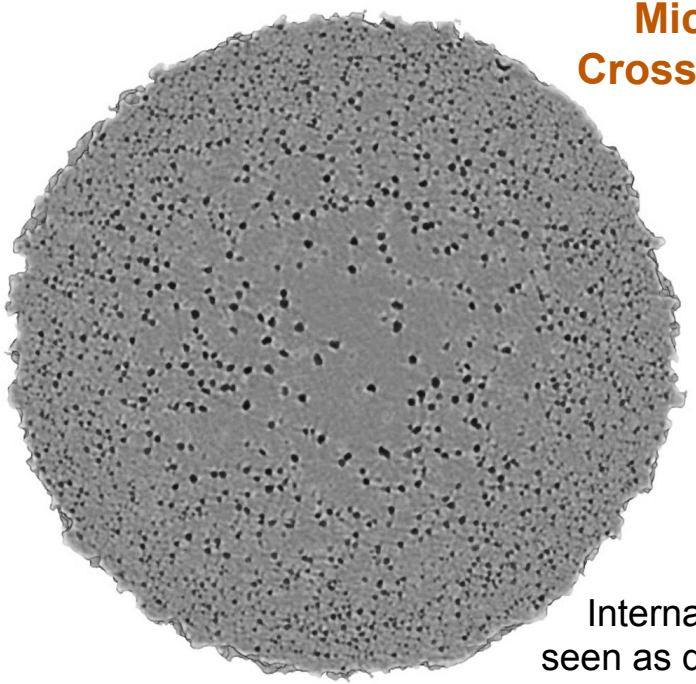


MicroCT Cross-section

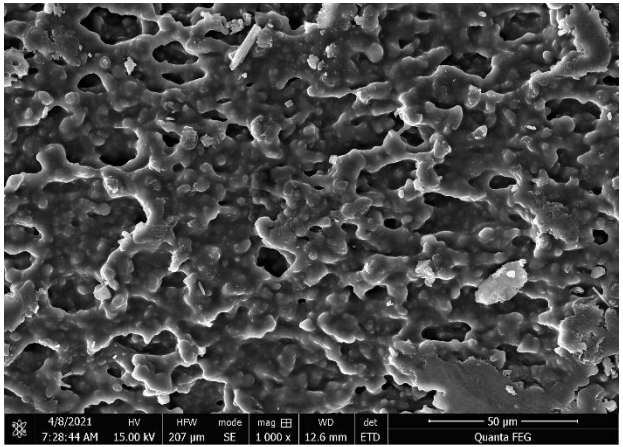


Internal voids seen as dark spots

Structural analysis of Ozurdex

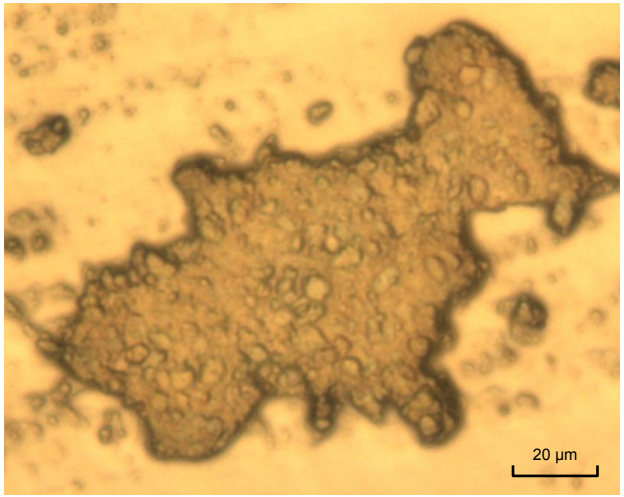
SEM, PLM, and DSC reveal 2-phase system with limited interaction between dexamethasone and PLGA

SEM of Implant Surface



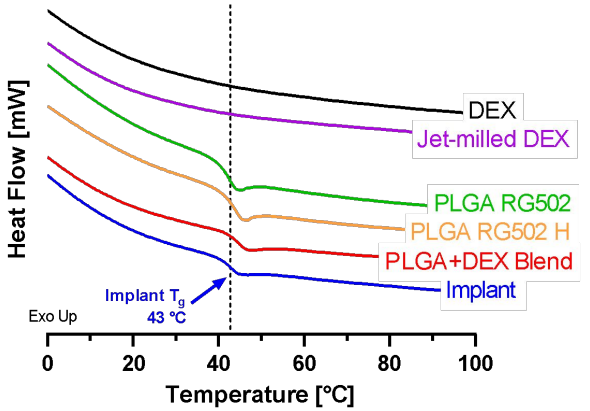
Few DEX crystals on surface, largely embedded in PLGA matrix

Hot stage PLM



DEX crystalline under PLM, estimated d(50) = 2 µm

DSC



No change to PLGA T_g after melt extrusion at 105°C

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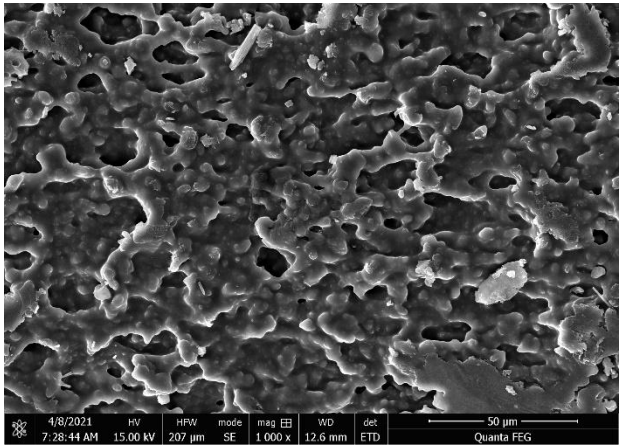

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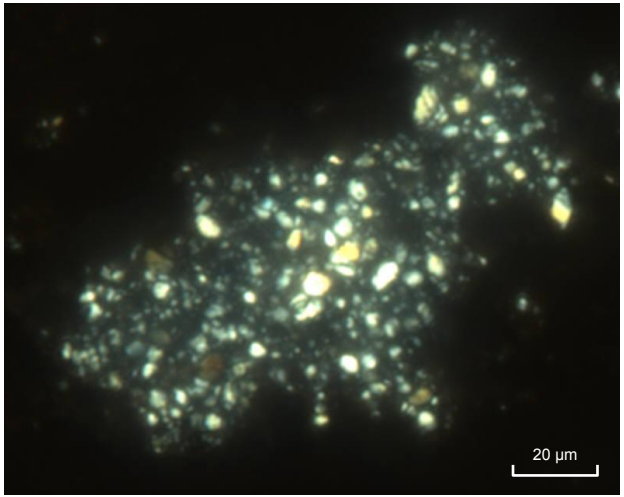

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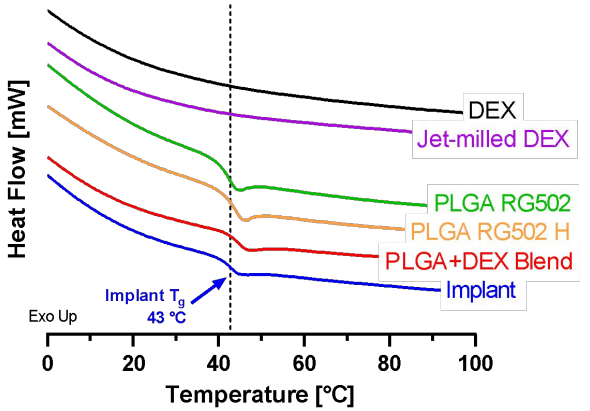


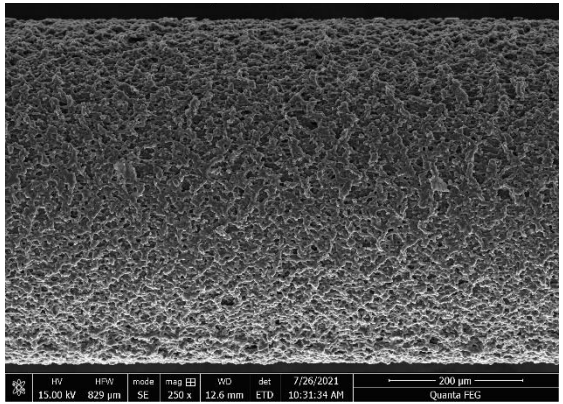
No change to PLGA T_g after melt extrusion at 105°C

Reverse engineering of Ozurdex

2-stage hot melt extrusion process developed to produce implants for further study

Jet-mill PLGA and DEX → Powder blending → 1st Extrusion (densification) → Milling (granules) → 2nd Extrusion & Implant Shaping → Manually cut to length

SEM profile
(UT-Austin Prototype)



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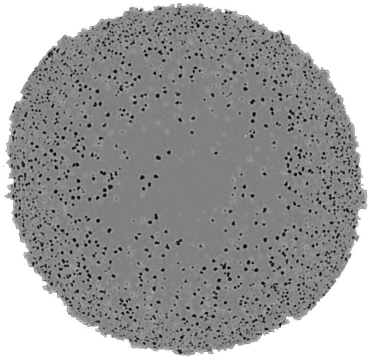
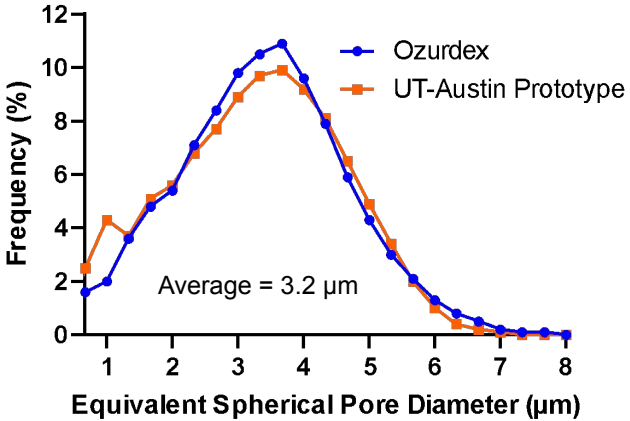


Pore Size Comparison

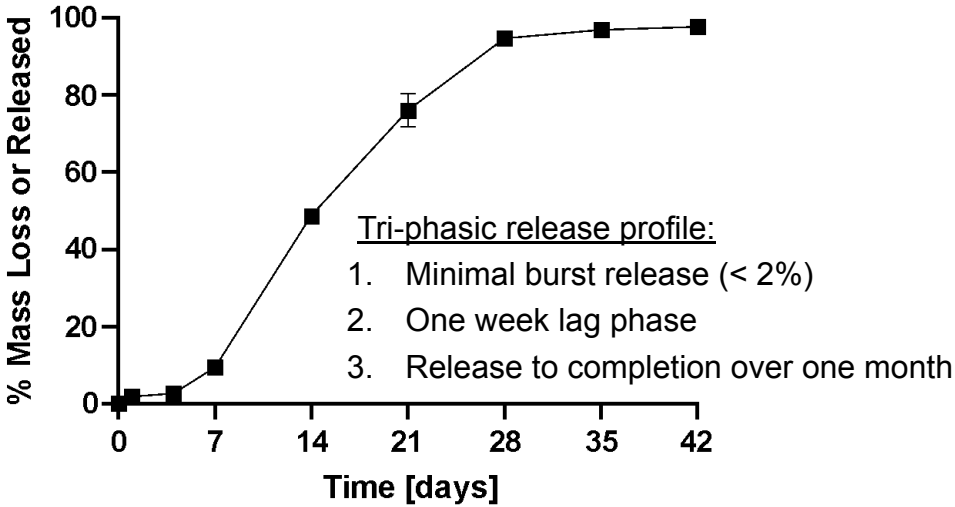


Shiah J-G, Bhagat R, Blanda WM, Nivaggioli T, Peng L, Chou D, et al., inventors; Allergan, Inc., assignee. Ocular implant made by a double extrusion process. USA patent US8034366. 2011.

In vitro release testing in normal saline of DEX implants

Tri-phasic release profile aligns with published data

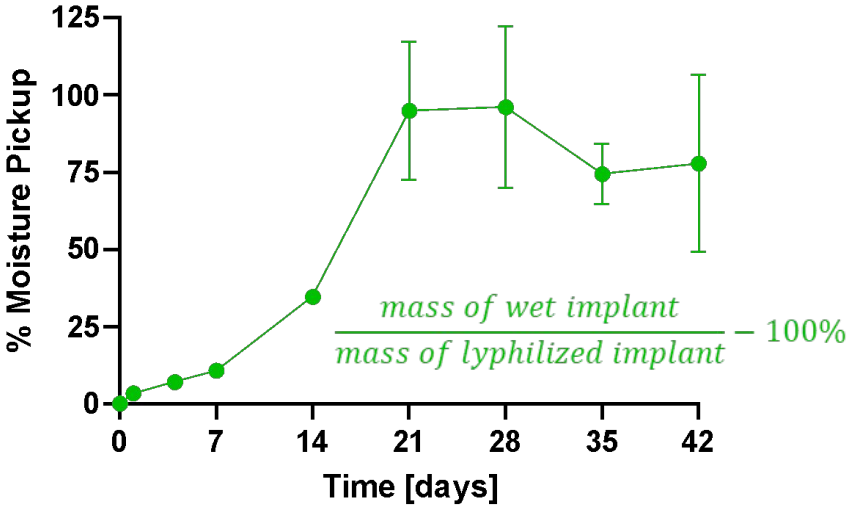
Dexamethasone Intravitreal Implant Dissolution
37°C, 30 mL, Normal Saline, N=6 (mean ± S.D.)



Tri-phasic release profile:

1. Minimal burst release (< 2%)
2. One week lag phase
3. Release to completion over one month

Moisture Pickup during Dissolution
37°C, 30 mL, Normal Saline, N=6 (mean ± S.D.)



Bhagat R, Zhang J, Farooq S, Li XY. Comparison of the release profile and pharmacokinetics of intact and fragmented dexamethasone intravitreal implants in rabbit eyes. J Ocul Pharmacol Ther. 2014;30(10):854-8.
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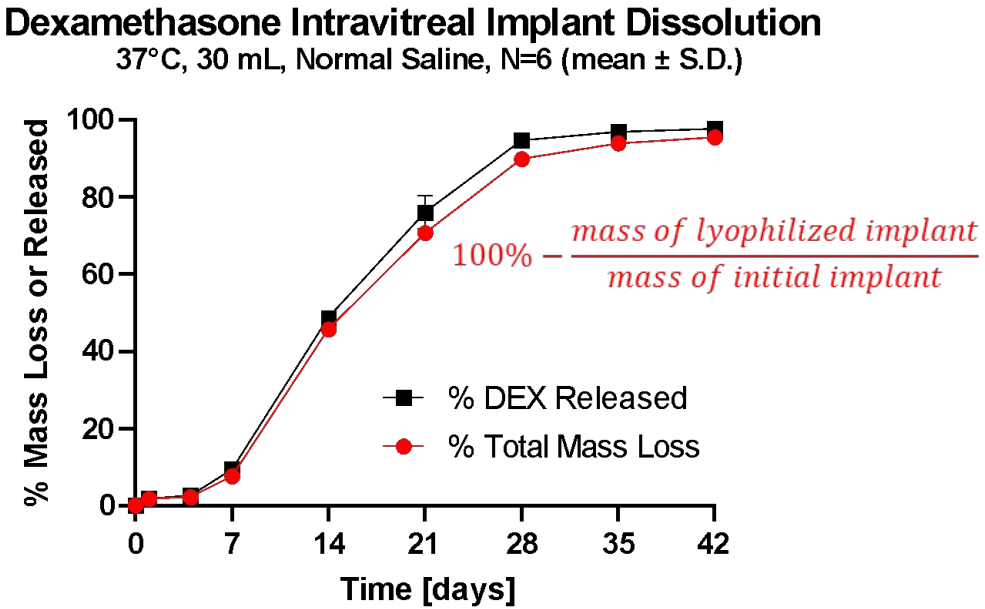

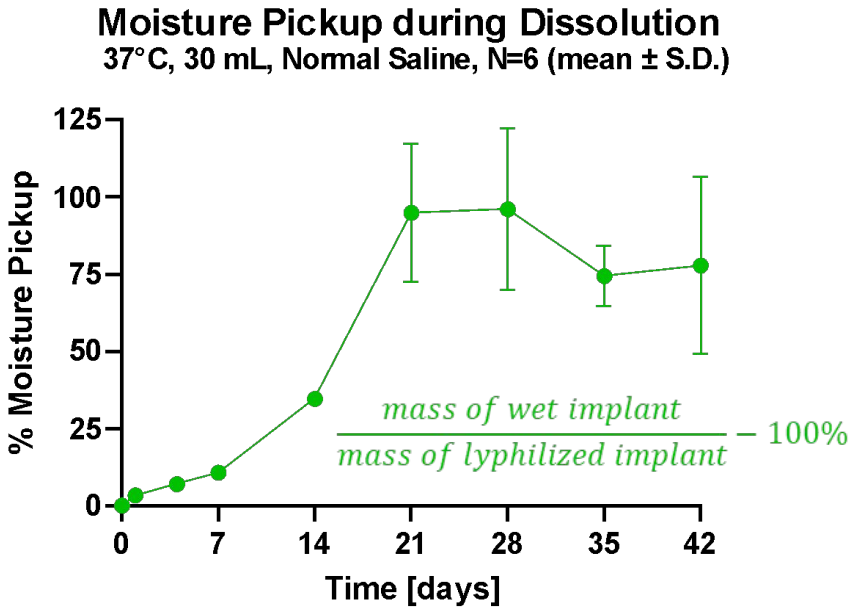

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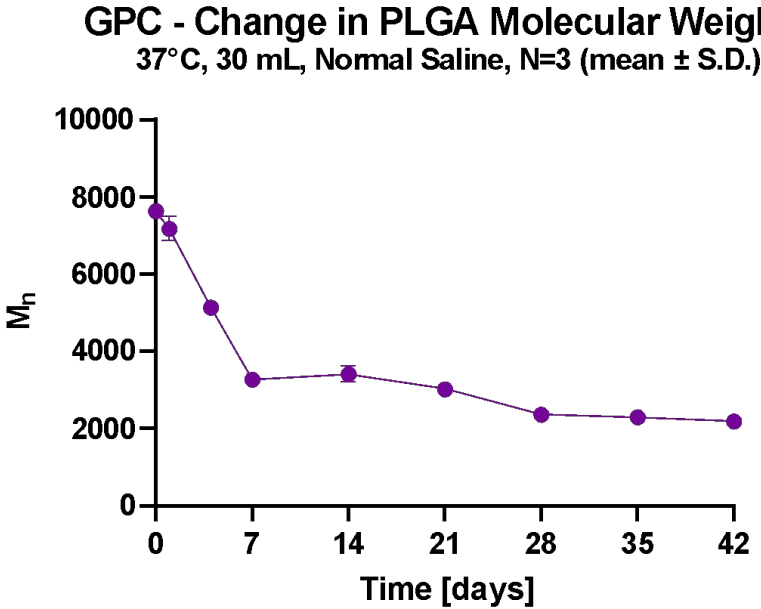
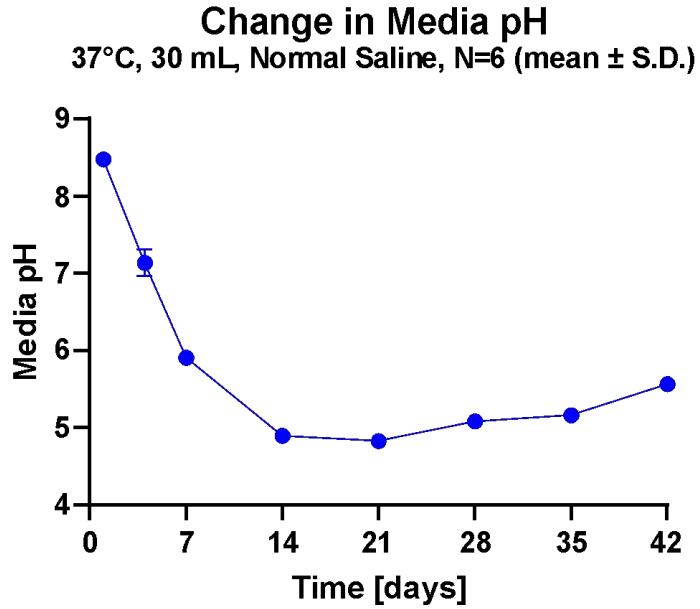
In vitro release testing in normal saline of DEX implants

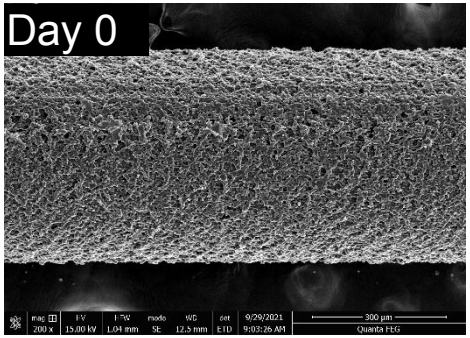
Limited drug release in first week despite substantial changes to the implant

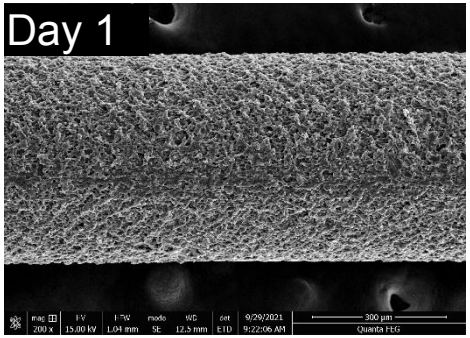


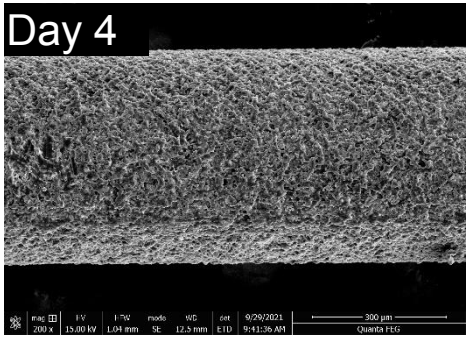


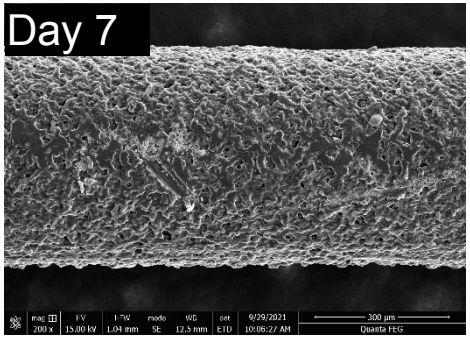
In vitro release testing in normal saline of DEX implants

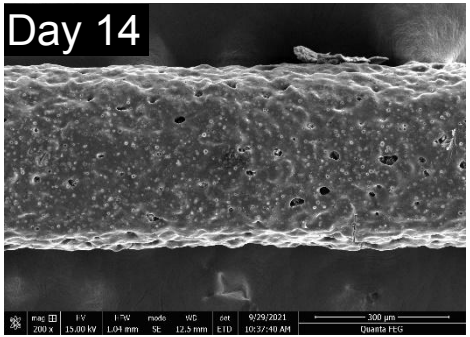
SEM (after lyophilization) shows significant structural changes to implant after day 7

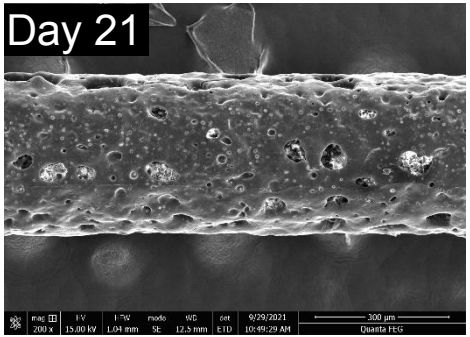


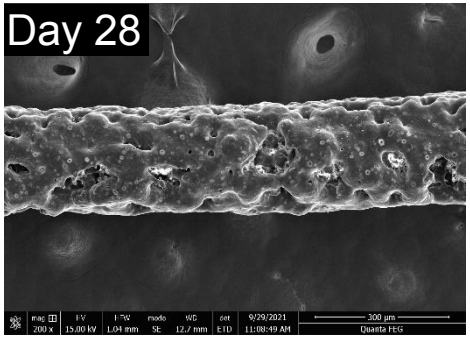


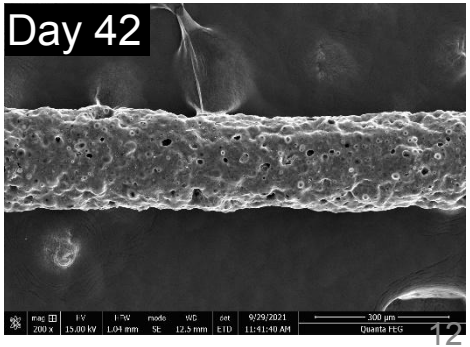












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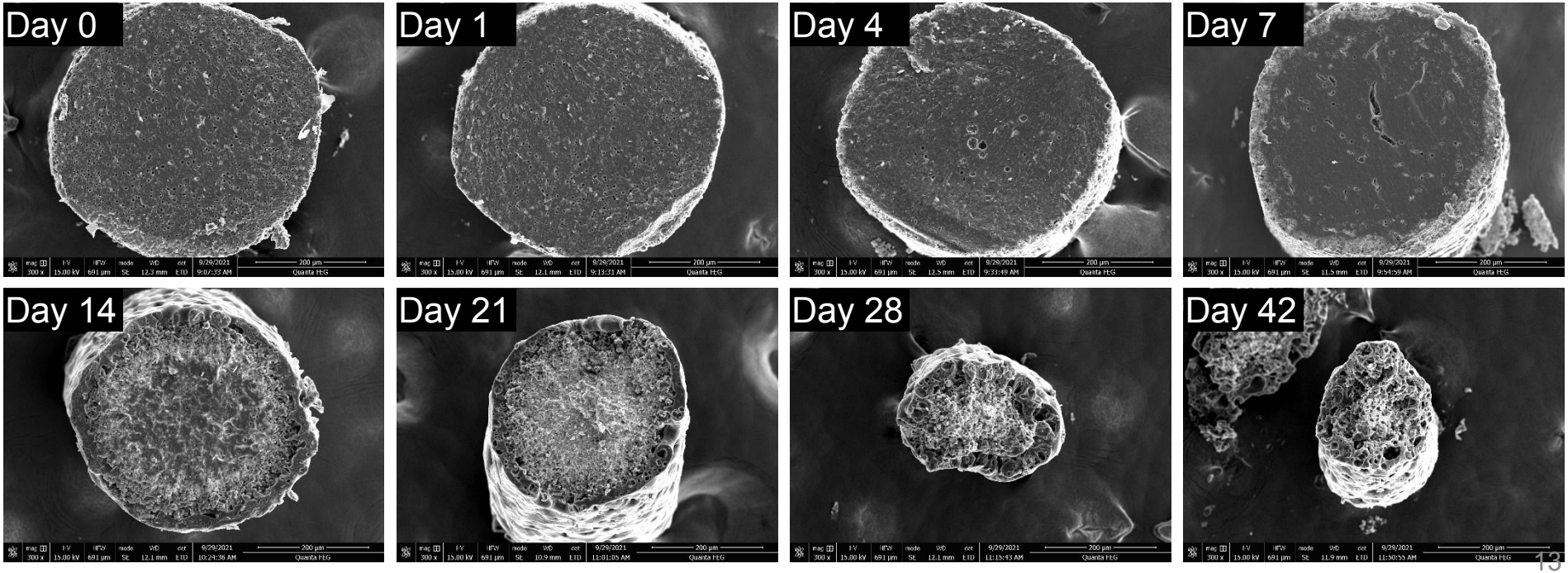
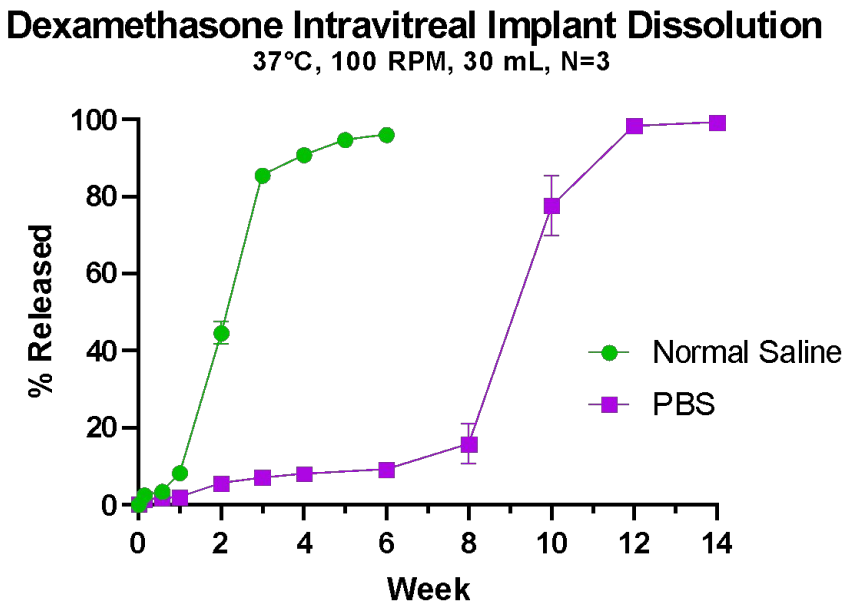


Drug release mechanisms of dexamethasone intravitreal implants

Tri-phasic profile derives from implant structure and chemical properties of DEX/PLGA

- Limited solubility of DEX in PLGA results in DEX crystals uniformly dispersed throughout the PLGA matrix after melt extrusion
- Little burst release observed due to inaccessibility of DEX crystals coated in PLGA on implant surface
- Low aqueous solubility of DEX (90 µg/mL) contributes to slow release, even in the presence of water, during the lag phase



Acknowledgements

TEXAS Pharmacy

- Dr. Feng Zhang, Associate Professor
- Dr. Beibei Chen, Postdoc
- Joseph Liu, Undergraduate student

U.S. Food & Drug Administration,
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Office of Generic Drugs, CDER

- Dr. Bin Qin, Staff Fellow
- Dr. Yan Wang, Team Lead

MARK COSTELLO
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Department of Molecular Pharmaceutics & Drug Delivery

Check out poster # **313** regarding manufacture and process control of dexamethasone intravitreal implants produced by hot melt extrusion