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TEXAS
The University of Texas at Austin

MELT-EXTRUDED DEXAMETHASONE OPHTHALMIC IMPLANTS: PROCESS, STRUCTURE AND IN VITRO DRUG RELEASE

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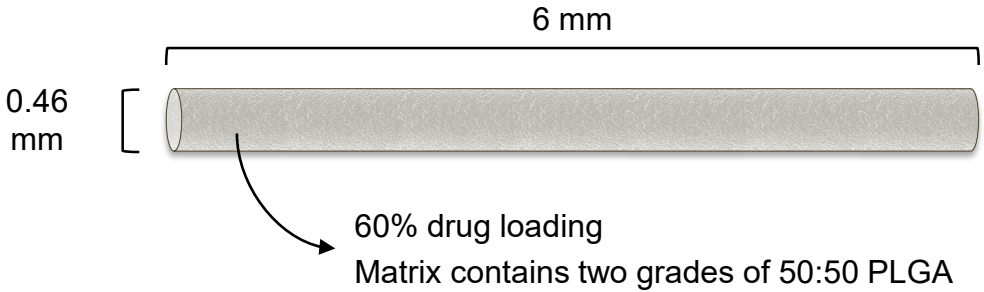
San Diego, CA

Dexamethasone (DEX) Ophthalmic Implant

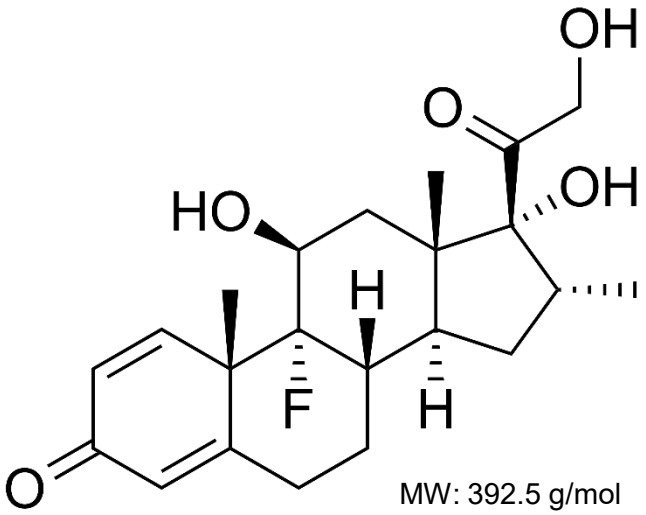


Component	% wt	wt. (mcg)/implant
Dexamethasone, Form B (micronized)	60	700
50:50 PLGA ester with acid end group	30	350
50:50 PLGA ester with ester end group	10	116

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 10/11/2011.

Dexamethasone

- Anti-inflammatory corticosteroid
- Poor aqueous solubility: 90 µg/mL
- LogP: 1.83
- Non-ionizable
- T_m = 265 °C
- Two crystalline forms: A and B

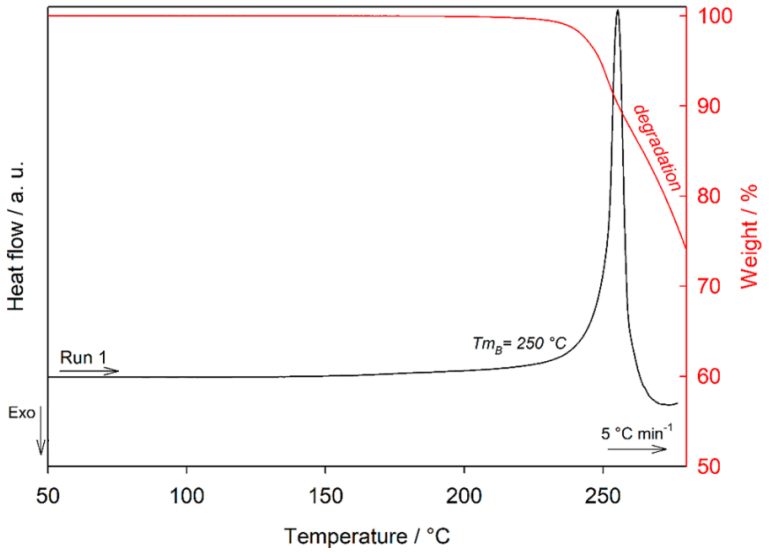


MW: 392.5 g/mol

http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=022315
https://pubchem.ncbi.nlm.nih.gov/compound/Dexamethasone
Oliveira PFM, Willart J-F, Siepmann J, Siepmann F, Descamps M. Using Milling To Explore Physical States: The Amorphous and Polymorphic Forms of Dexamethasone. Crystal Growth & Design. 2018;18(3):1748-57.

DEX degrades upon melting

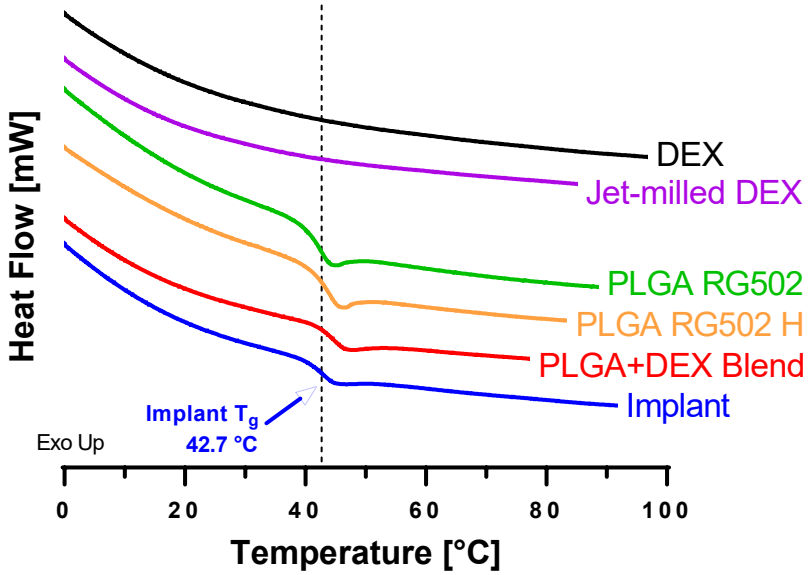
- TGA shows significant degradation of DEX occurs once it melts
- No weight loss below 150°C
- Melt temp for melt extrusion of ophthalmic implant: 100-110°C



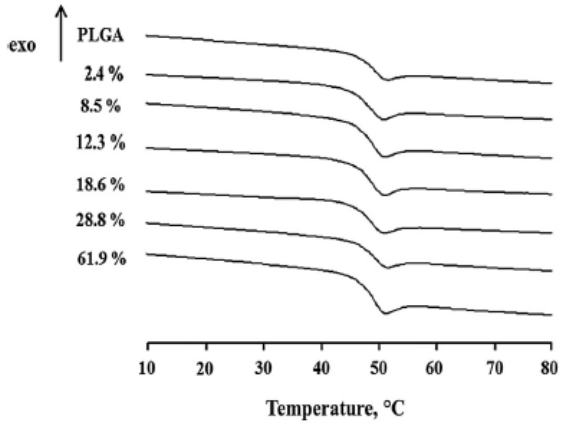
Oliveira PFM, Willart J-F, Siepmann J, Siepmann F, Descamps M. Using Milling To Explore Physical States: The Amorphous and Polymorphic Forms of Dexamethasone. Crystal Growth & Design. 2018;18(3):1748-57.

Little interaction between DEX and PLGA

DEX does not depress PLGA T_g



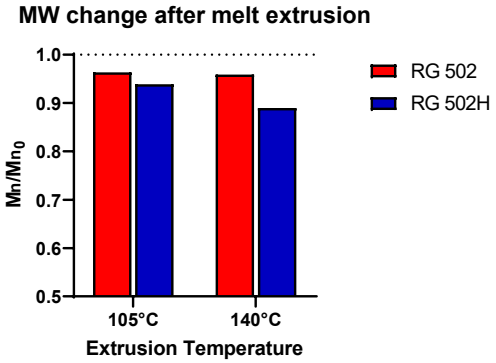
DEX + PLGA microspheres
(various drug load)

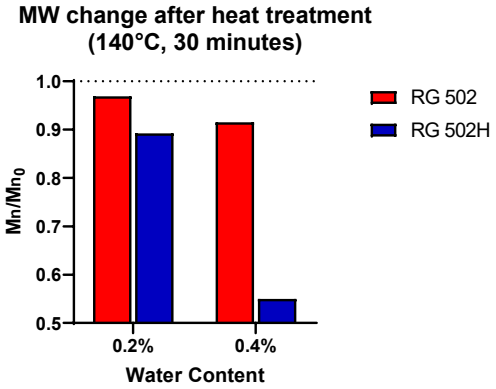


Gasmi H, Siepmann F, Hamoudi MC, Danede F, Verin J, Willart JF, et al. Towards a better understanding of the different release phases from PLGA microparticles: Dexamethasone-loaded systems. Int J Pharm. 2016;514(1):189-99.

PLGA thermally stable below 140°C

- PLGA can degrade by hydrolysis and thermal mechanisms
- TGA shows thermal degradation is not significant below 200°C
- RG502 and RG502 H PLGAs were demonstrated to be stable below 140°C during HME
- Adsorbed moisture accelerates degradation of RG502 H > 30% RH

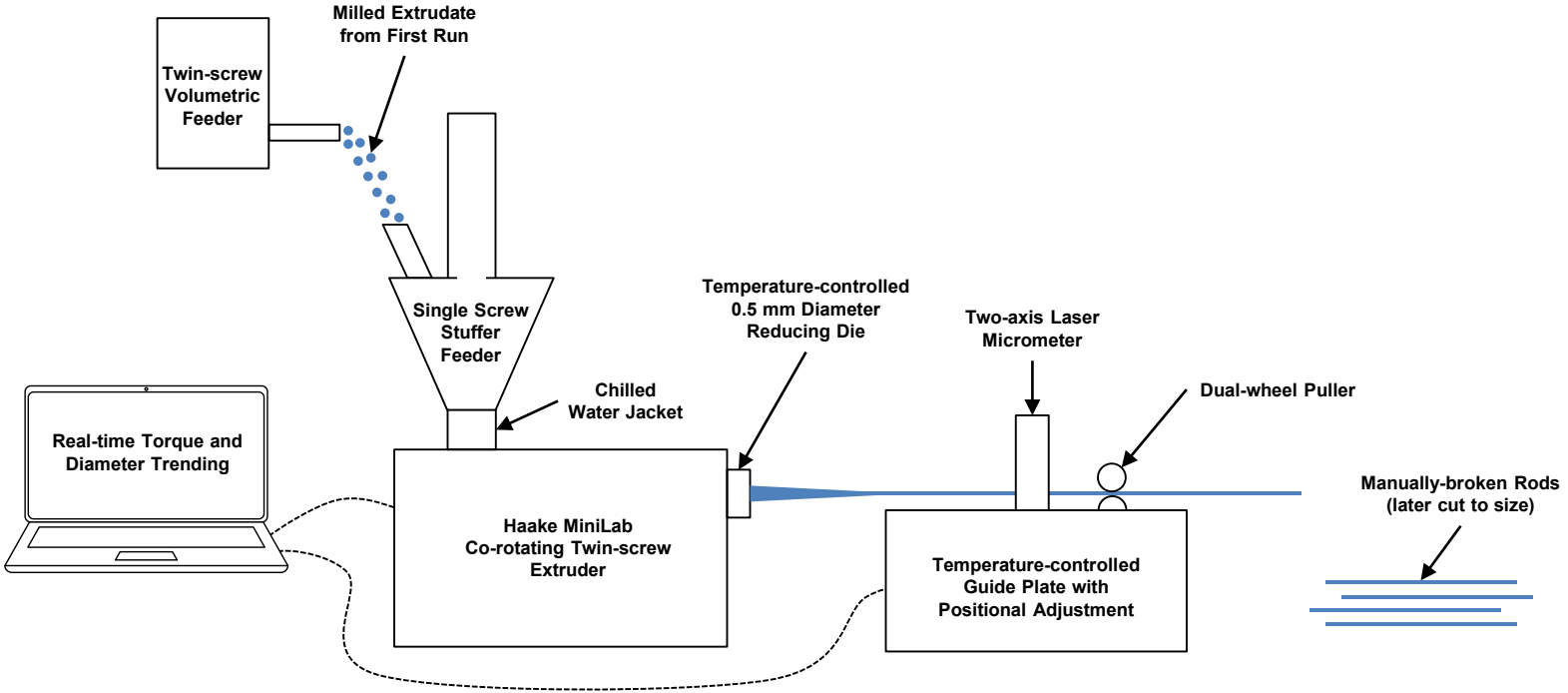




Chen, B. Investigation of the thermal stability and hydrolytic degradation kinetics of poly(lactide-co-glycolide) melts. 2022. Unpublished.

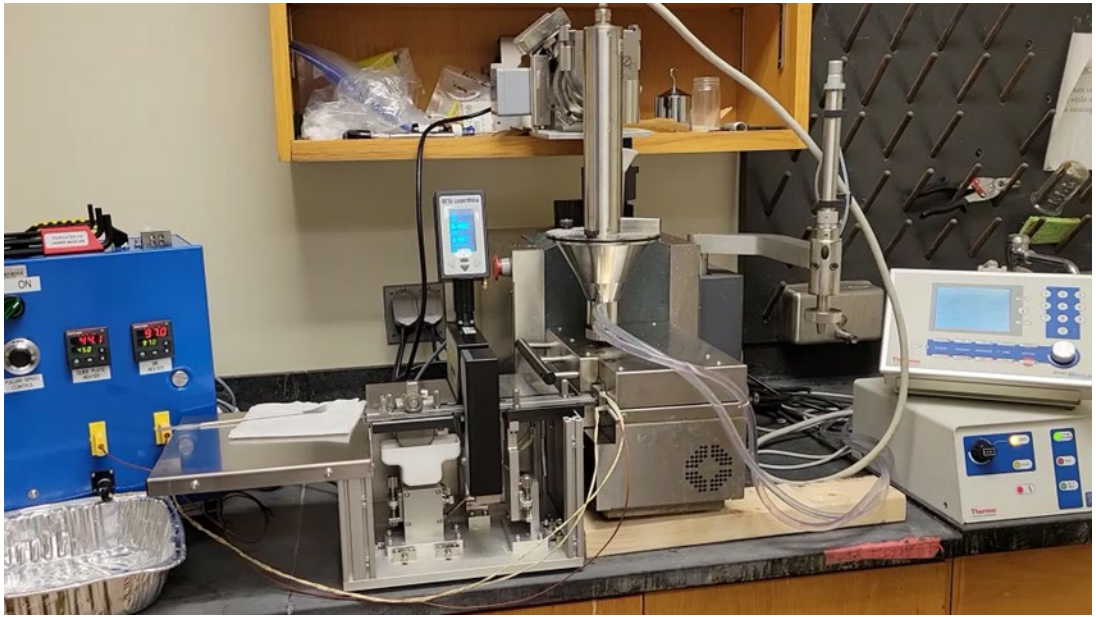
In-house DEX implant manufacturing process

Schematic

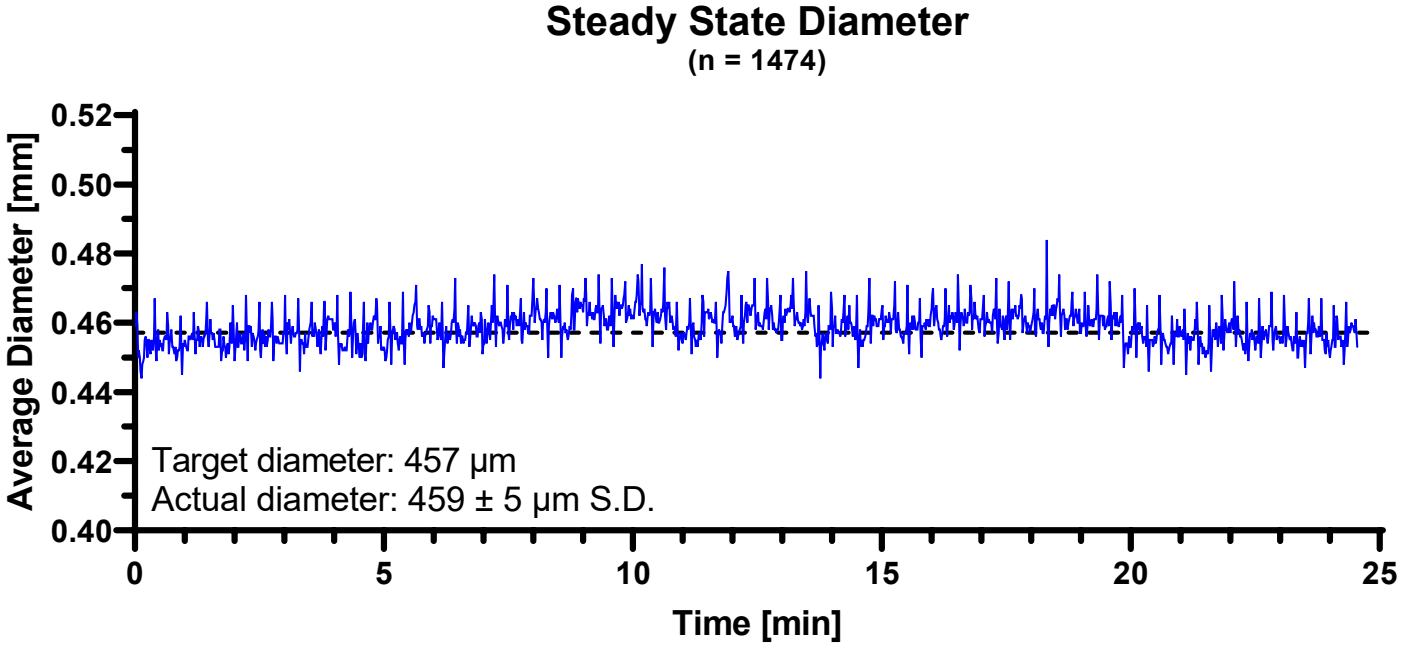


In-house ocular implant manufacturing process

Video



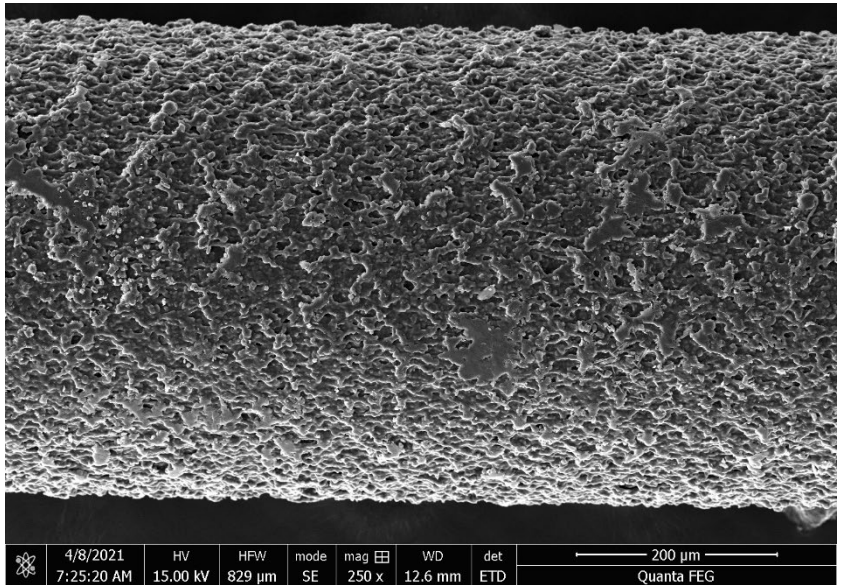
Accurate diameter control achieved with 2-stage feeding



Structural analysis of DEX implant

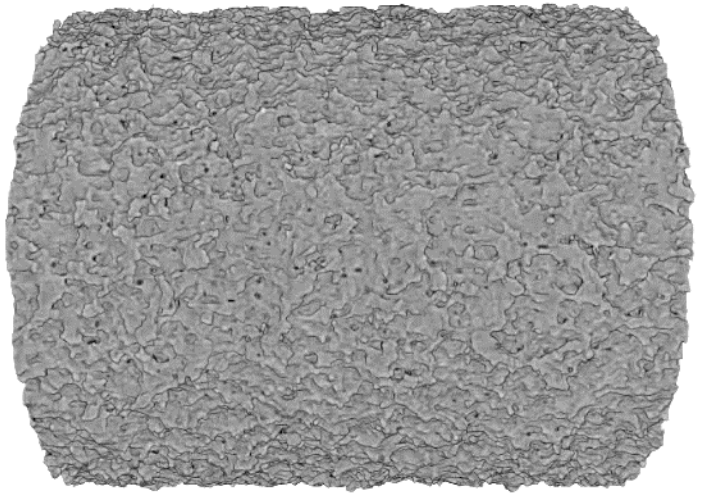
SEM and MicroCT reveal irregular surface and 6% internal porosity

SEM profile



MicroCT profile

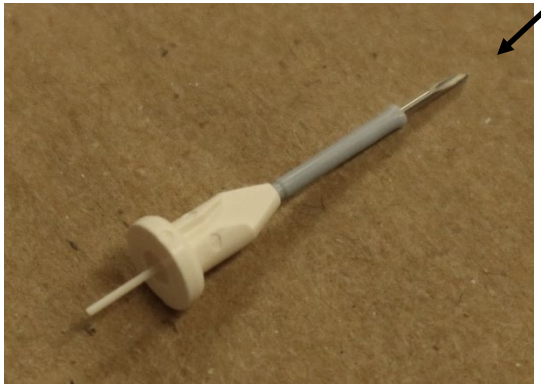
MicroCT Cross-section



Internal voids seen as dark spots

2-step extrusion process for implant structure control

First extrusion densifies jet-milled blend → Milled into granules with Improved bulk flow → More consistent feeding into extruder → More consistent flow at extruder die → Better diameter control during drawdown → Appropriate fit in applicator needle



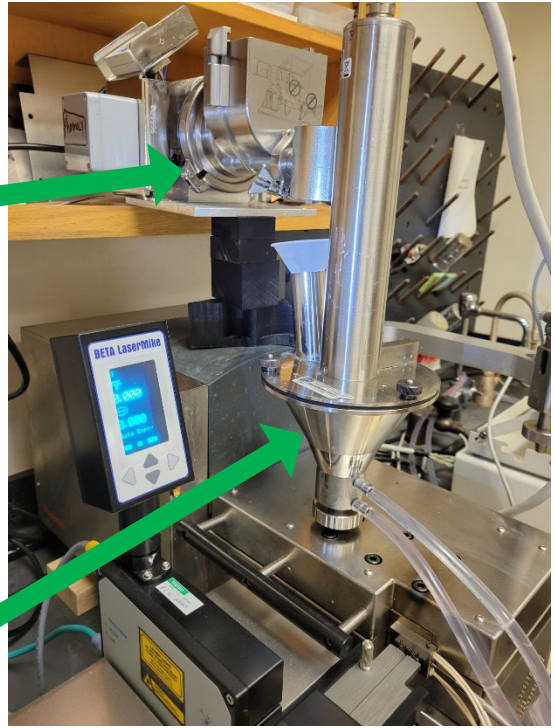
2-stage feeding process to achieve consistent feed rate (8-10 g/hr)

Possible solutions to improve feeding performance of Haake force feeder

1. Volumetric/gravimetric feeder → granules bridge over screws, need stuffer feeder
2. Force feeder with more powerful motor
3. **Combination of volumetric (Brabender) and stuffer feeding (Haake)**

Stage 1: Brabender twin-screw volumetric feeder

Stage 2: Haake force feeder (water-cooled jacket to just above dew point)

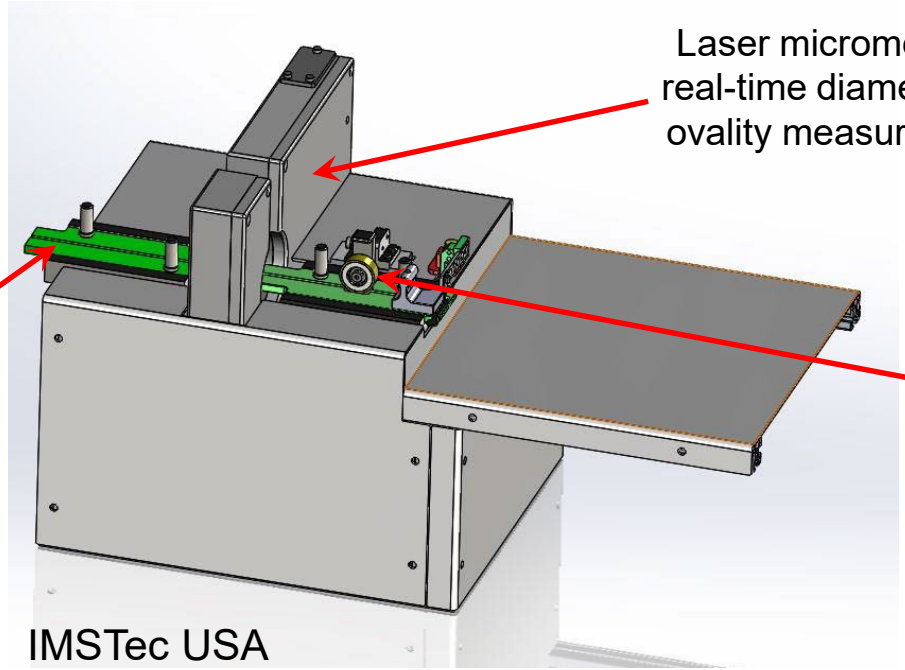


Puller for controlled drawdown to target diameter

Purpose-built unit for fine adjustment of drawdown parameters

Laser micrometer for real-time diameter and ovality measurements

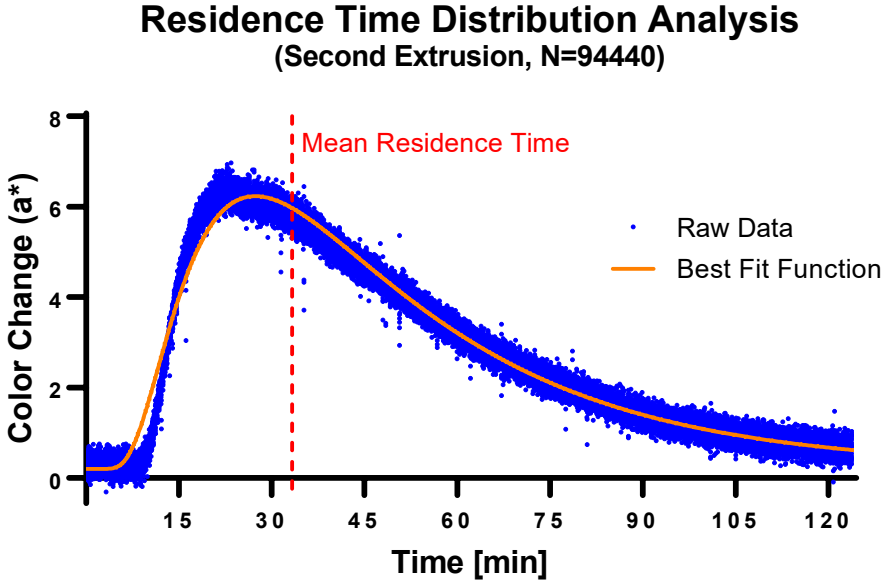
Heated guide plate to maintain extruded rod flexibility during drawdown to target diameter



Dual-wheel puller with adjustable speed to drawdown extrudate to desired diameter

Long residence time observed due to need for slow and steady feeding (8-10 g/hr)

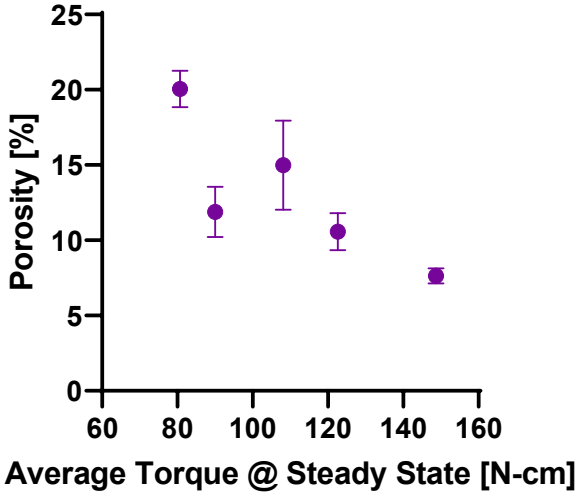
- Mean residence time = 33 min
  - Used tracer dye and laboratory camera to detect color change
  - In-house software developed for data acquisition and analysis
- Assay confirms DEX stability and uniformity
  - Potency: 100.1 ± 0.2% SD (N=6)
- GPC data shows 7% reduction in M_n

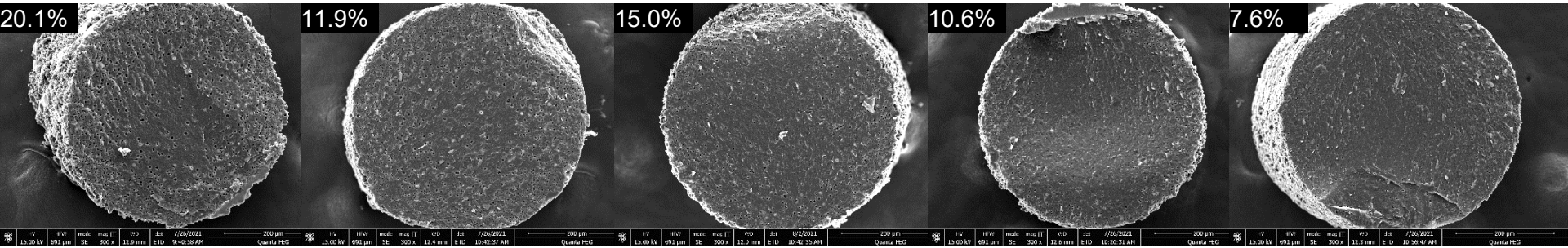


Wahl PR, Hörl G, Kaiser D, Sacher S, Rupp C, Shlieout G, et al. In-line measurement of residence time distribution in melt extrusion via video analysis. Polymer Engineering & Science. 2018;58(2):170-9.

Steady-state torque correlates with implant porosity

Steady-state torque can be thought of as extruder back-pressure





Increasing steady-state torque

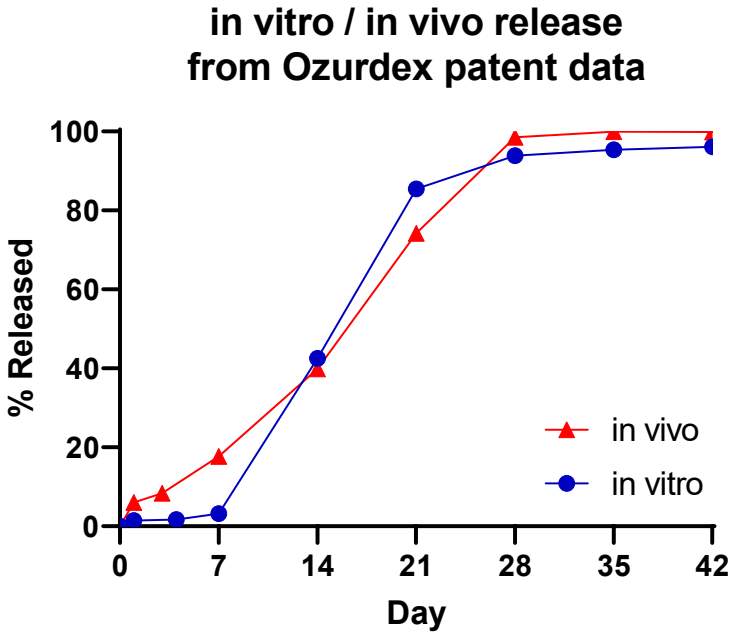
DEX Ophthalmic Implant – Process and Structure

- Low glass transition temperature of PLGA enables the extrusion at relatively low temperature to maintain the chemical stabilities of dexamethasone
- Accurate diameter control was achieved with a two-step extrusion process using two-stage feeding design and a purpose-built downstream puller
- Various features of implant structure identified are:
  - diameter
  - pore size/distribution
  - surface roughness
- Preliminary data indicates that:
  - DEX does not dissolve in PLGA melt during extrusion and is dispersed in PLGA matrix as crystalline particles
  - DEX is stable during the current melt extrusion process

Dissolution testing of dexamethasone implant

Excerpt from patent

FIGS. 2 and 10 also demonstrate that after 28 days in vivo in rabbit eyes, or in vitro in a saline solution at 37°C., respectively, almost all of the active agent has been released from the implants. Furthermore, FIGS. 2 and 10 **show that the active agent release profiles for the extruded implants in vivo (from the time of implantation) and in vitro (from the time of placement into a saline solution at 37° C.) are substantially similar and follow approximately a sigmoidal curve, releasing substantially all of the active agent over 28 days.**



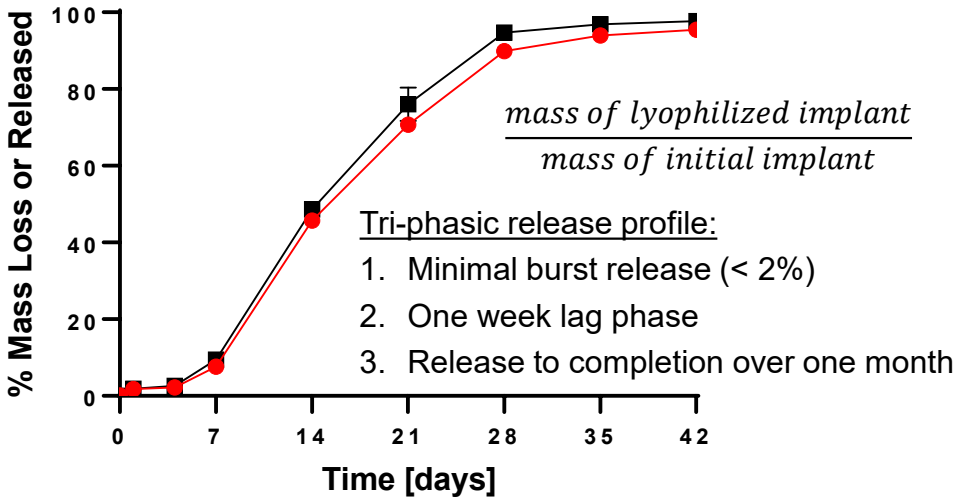
Replotted based on the data (Figs 2 and 10) in the patent

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 10/11/2011.
Bhagat R, Zhang J, Farooq S, Li X.Y. Comparison of the release profiles and pharmacokinetics of intact and fragmented dexamethasone intravitreal implant in rabbit eyes, Journal of Ocular Pharmacology and Therapeutics, 30 (10): 854-858 (2014)

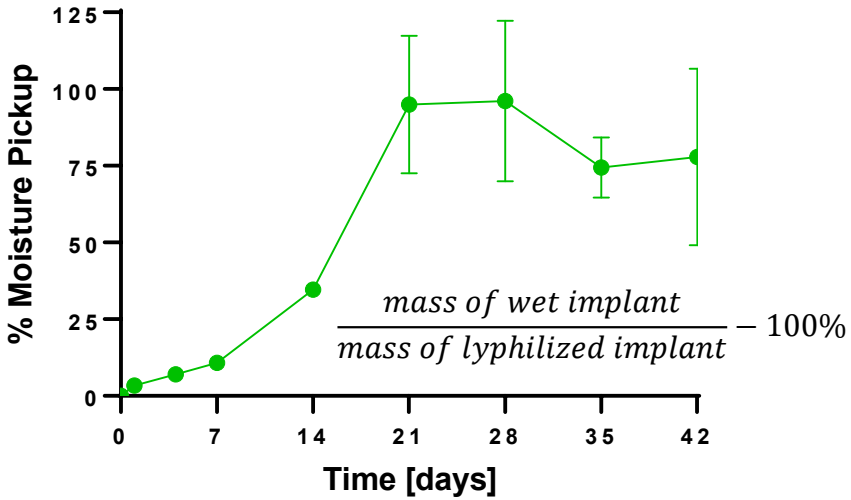
In vitro release testing in normal saline of DEX implants

Tri-phasic release profile aligns with published data

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



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



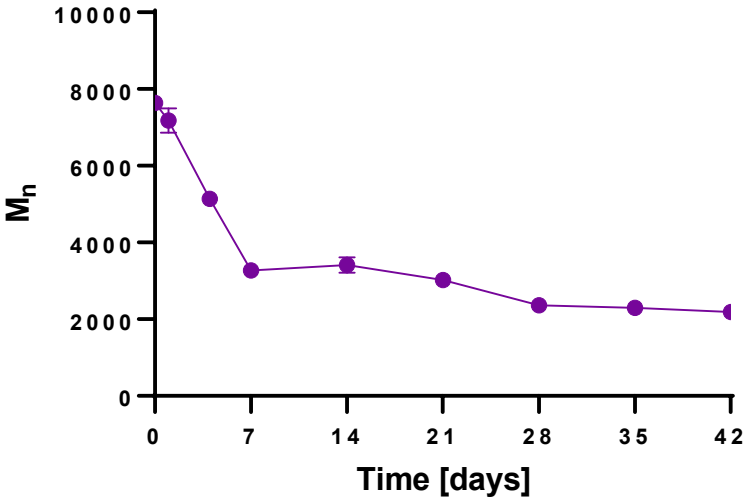
Bhagat R, Zhang J, Farooq S, Li XY. Comparison of the release profile and pharmacokinetics of intact and fragmented dexamethasone intravitreal implants in rabbit eyes. J Ocul Pharmacol Ther. 2014;30(10):854-8.
Tamani F, Bassand C, Hamoudi MC, Danede F, Willart JF, Siepmann F, et al. Mechanistic explanation of the (up to) 3 release phases of PLGA microparticles: Diprophylline dispersions. Int J Pharm. 2019;572:118819.

In vitro release testing in normal saline of DEX implants

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

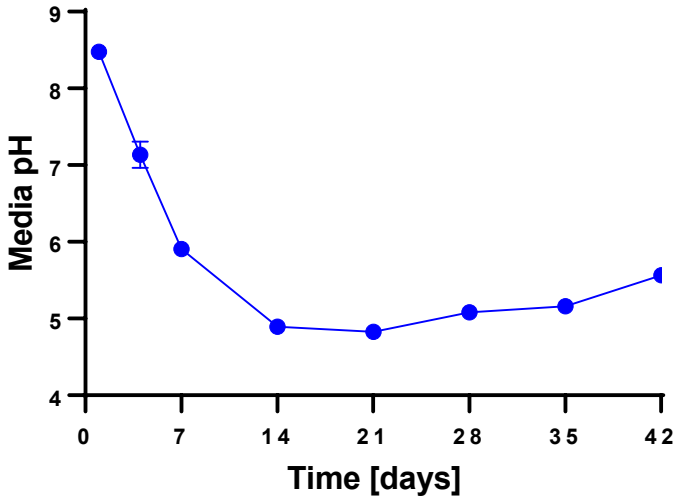
GPC - Change in PLGA Molecular Weight

37°C, 30 mL, Normal Saline, N=3 (mean ± S.D.)



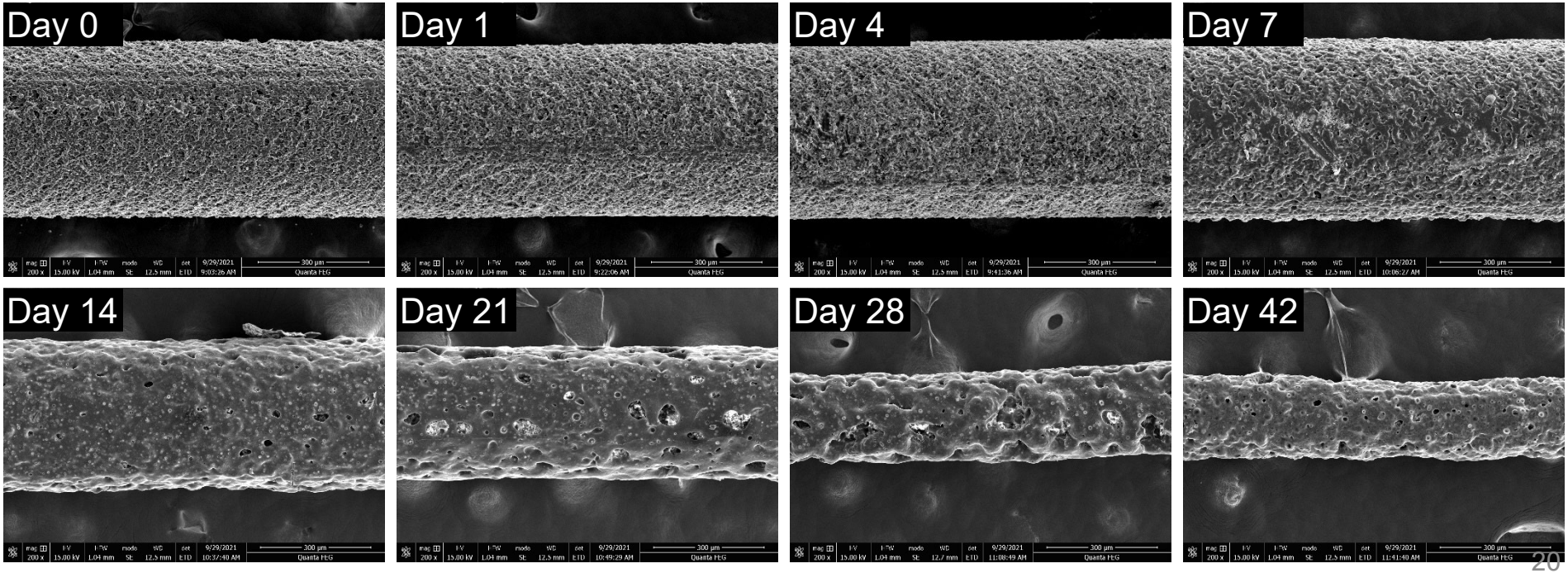
Change in Media pH

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



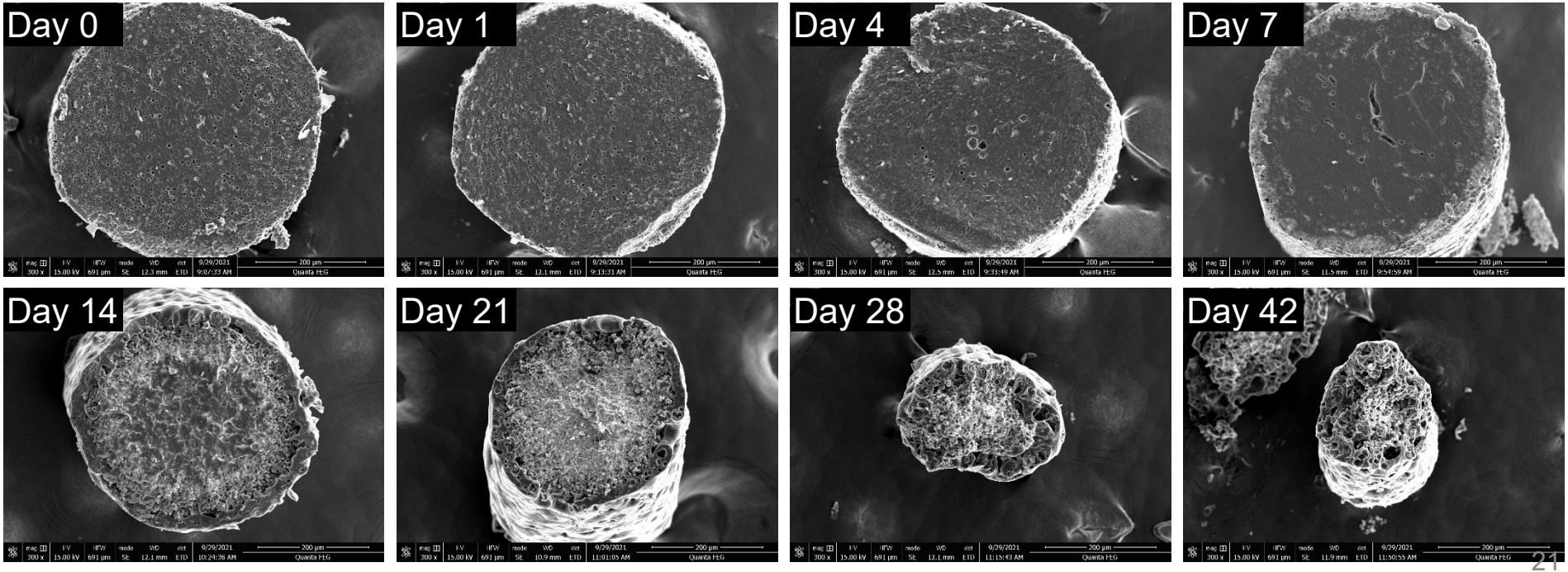
In vitro release testing in normal saline of DEX implants

SEM shows significant structural changes to implant after day 7

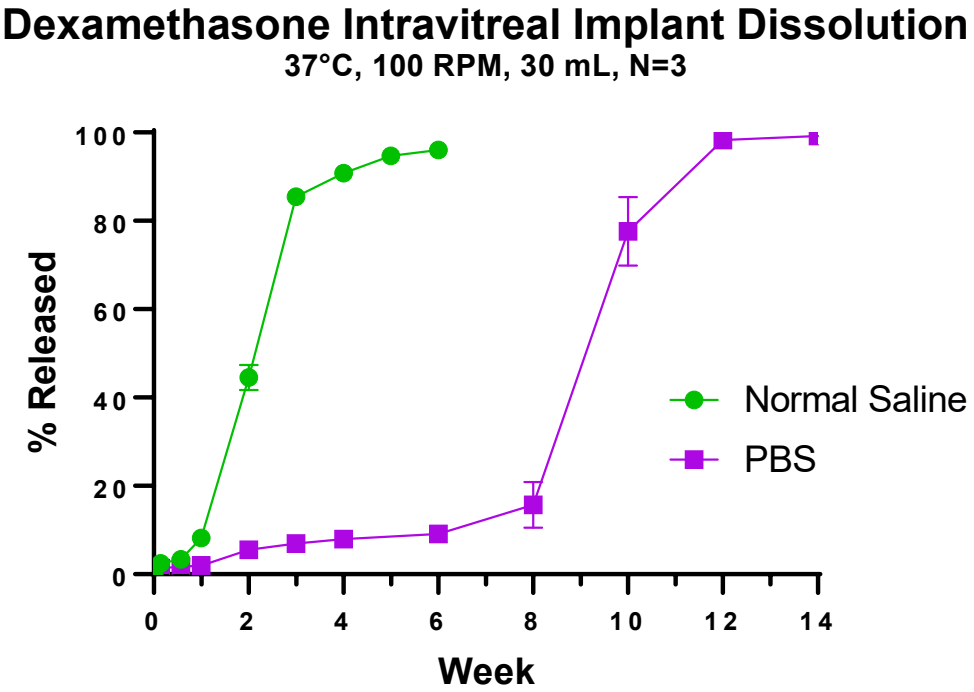


In vitro release testing in normal saline of DEX implants

SEM shows significant structural changes to implant after day 7



Similar tri-phasic release profile with slower release rate in phosphate buffer pH 7.4



DEX Ophthalmic Implant – Drug Release

- Tri-phasic profile derives from both implant structure and physicochemical interactions between DEX and PLGA
- Limited solubility of DEX in PLGA results in DEX crystals uniformly dispersed throughout the PLGA matrix after melt extrusion
- Burst release at the onset was not observed, due to inaccessibility of DEX crystals coated with PLGA on implant surface
- In the initial lag phase, significant PLGA undergoes significant hydrolysis even though less than 10% drug is released
- Dexamethasone release is controlled by the erosion of the implant matrix

Acknowledgements

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- Mark Costello, Graduate Student
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