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TEXAS
The University of Texas at Austin

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

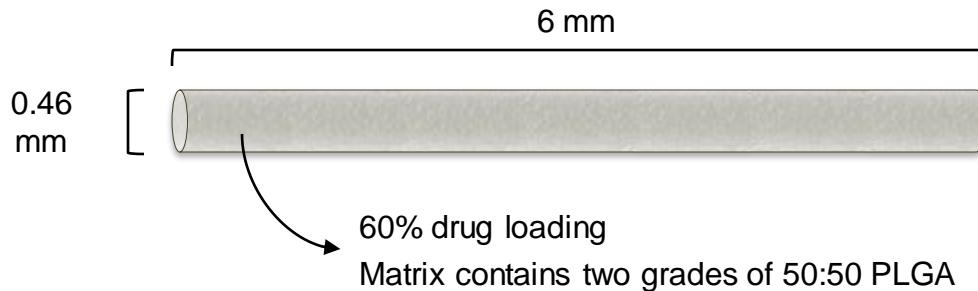
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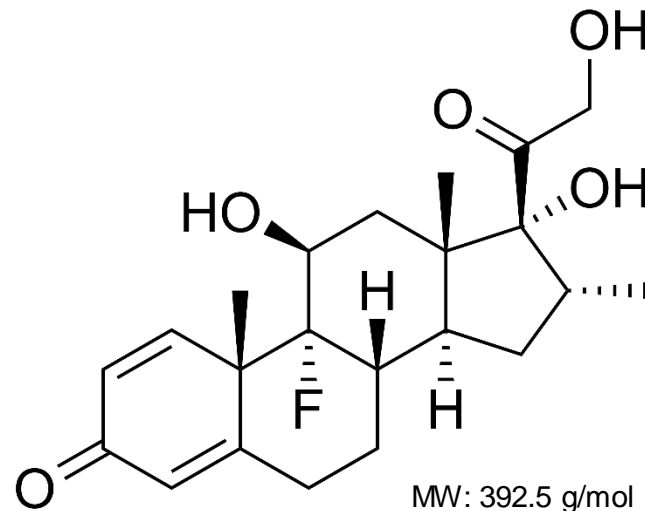
Dexamethasone (DEX) Ophthalmic Implant



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

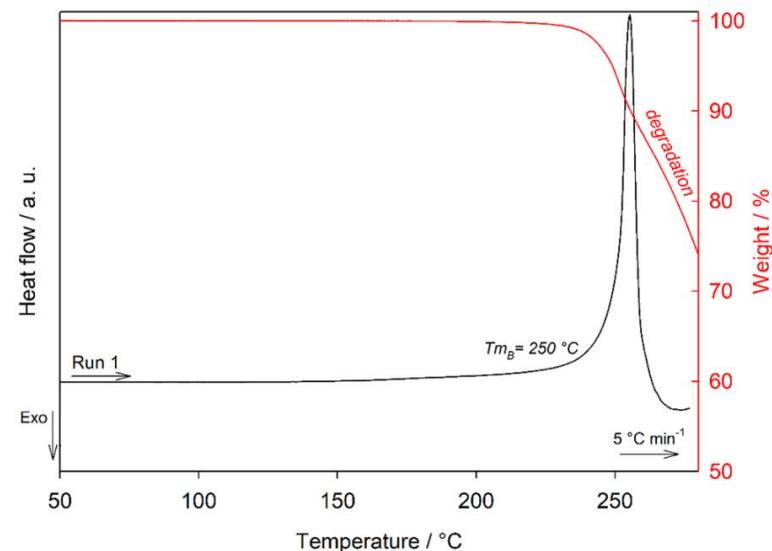
Dexamethasone

- Anti-inflammatory corticosteroid
- Poor aqueous solubility: 90 $\mu\text{g/mL}$
- LogP: 1.83
- Non-ionizable
- $T_m = 265\text{ }^\circ\text{C}$
- Two crystalline forms: A and B



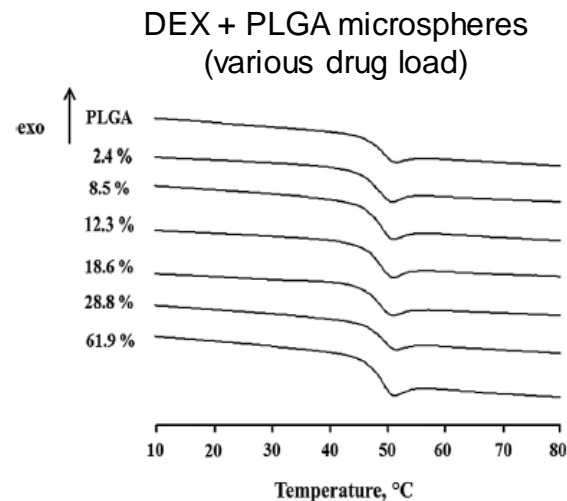
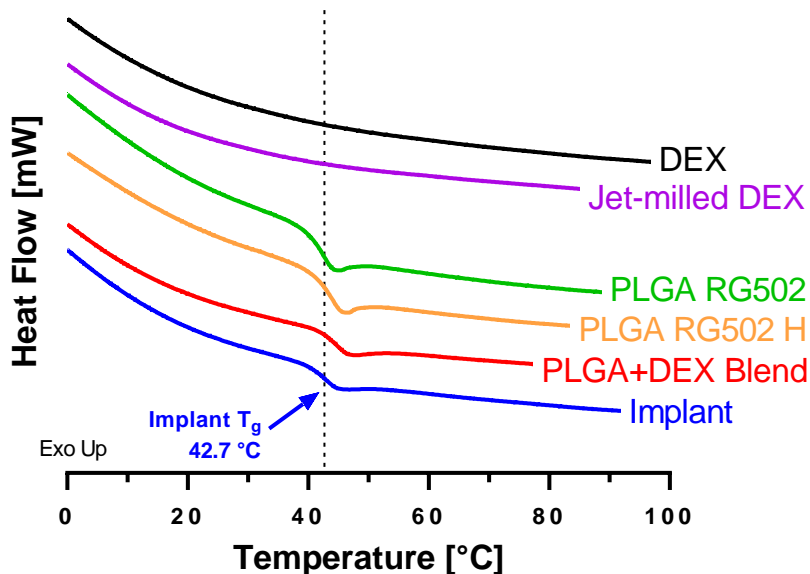
DEX degrades upon melting

- 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



Little interaction between DEX and PLGA

DEX does not depress PLGA T_g

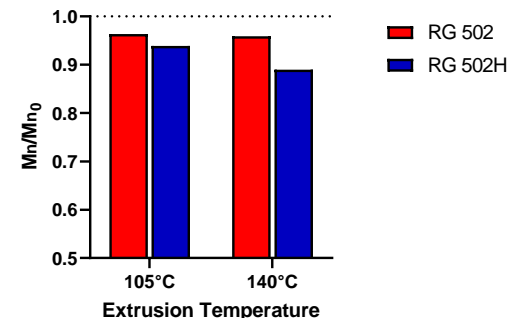


Gasmi H, Siepmann F, Hamoudi MC, Danede F, Verin J, Willart JF, et al. Towards a better understanding of the different release phases from PLGA microparticles: Dexamethasone-loaded systems. *Int J Pharm.* 2016;514(1):189-99.

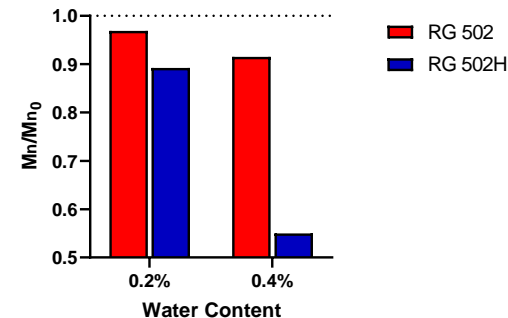
PLGA thermally stable below 140°C

- 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

MW change after melt extrusion

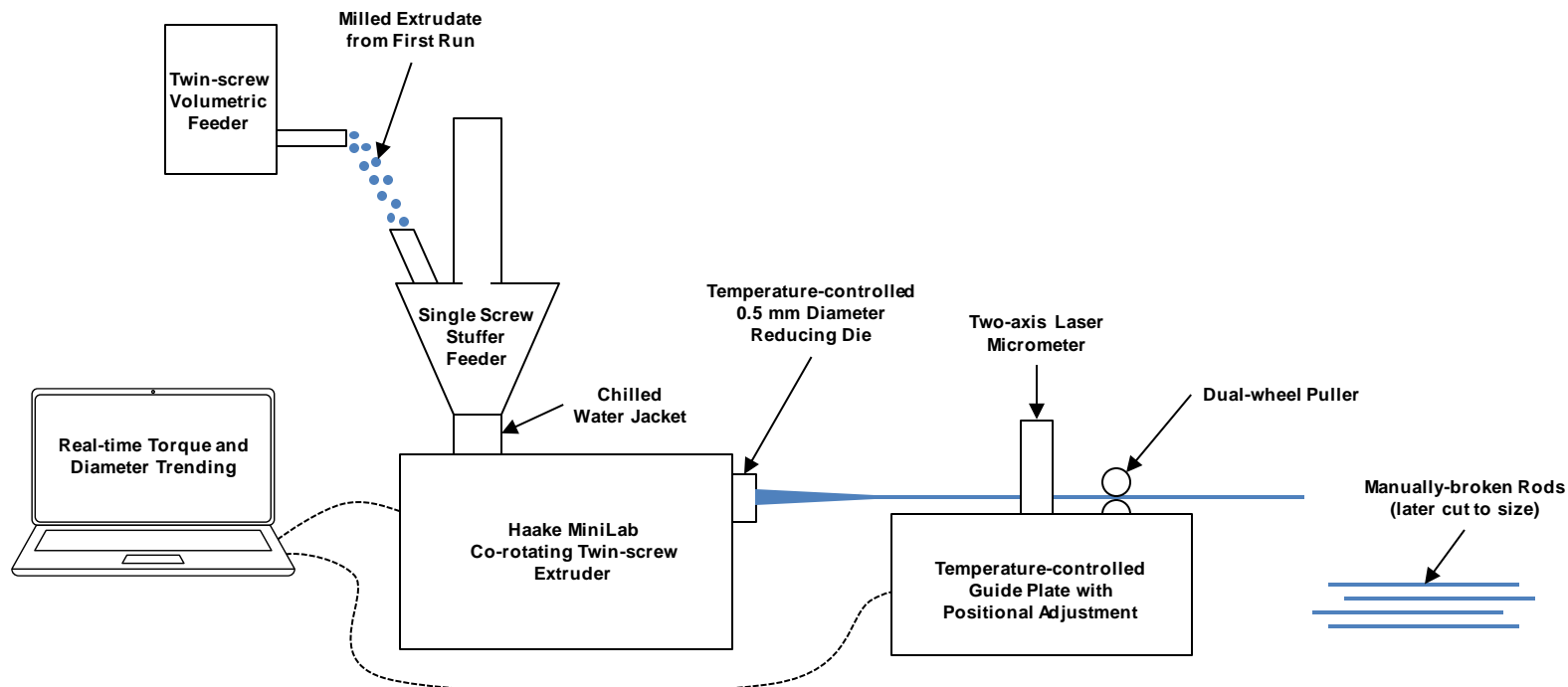


MW change after heat treatment (140°C, 30 minutes)



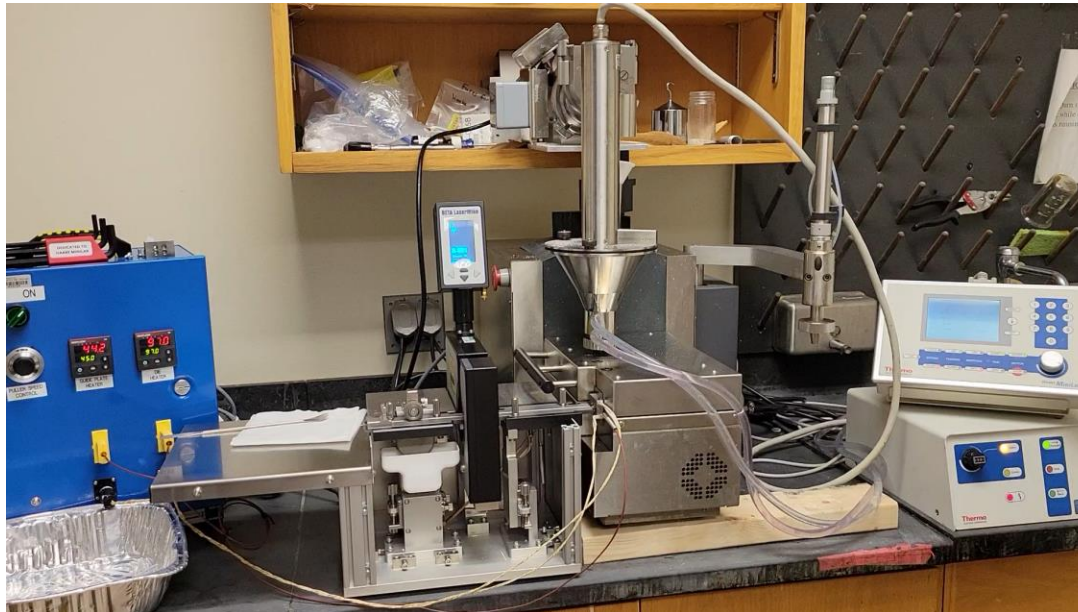
In-house DEX implant manufacturing process

Schematic



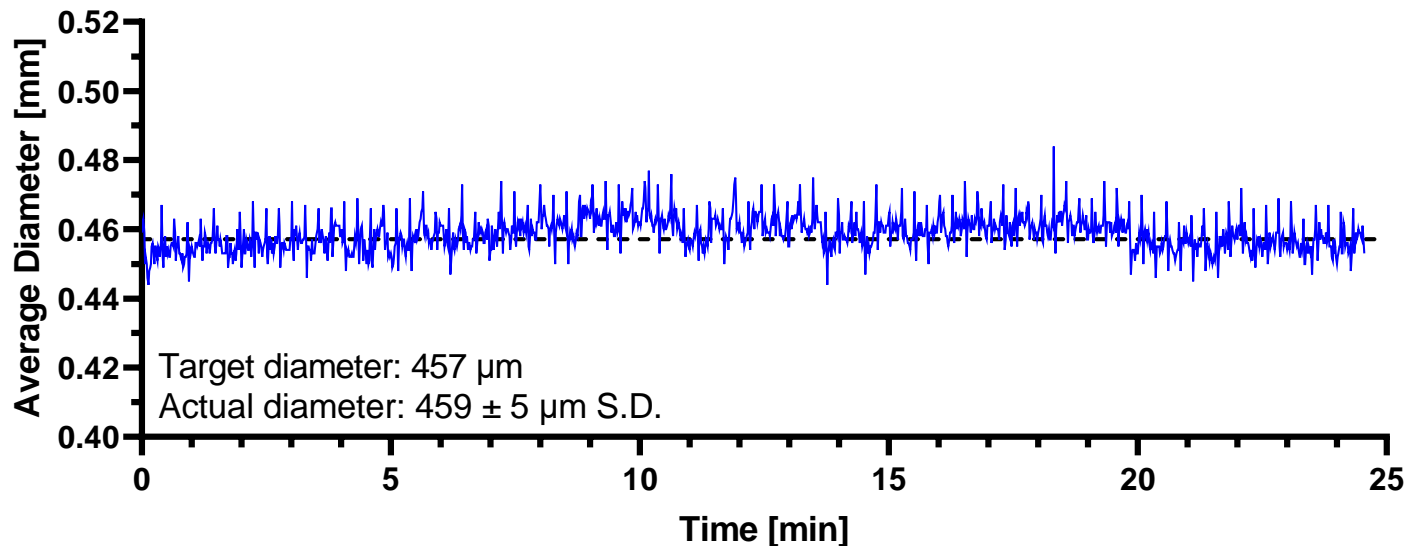
In-house ocular implant manufacturing process

Video



Accurate diameter control achieved with 2-stage feeding

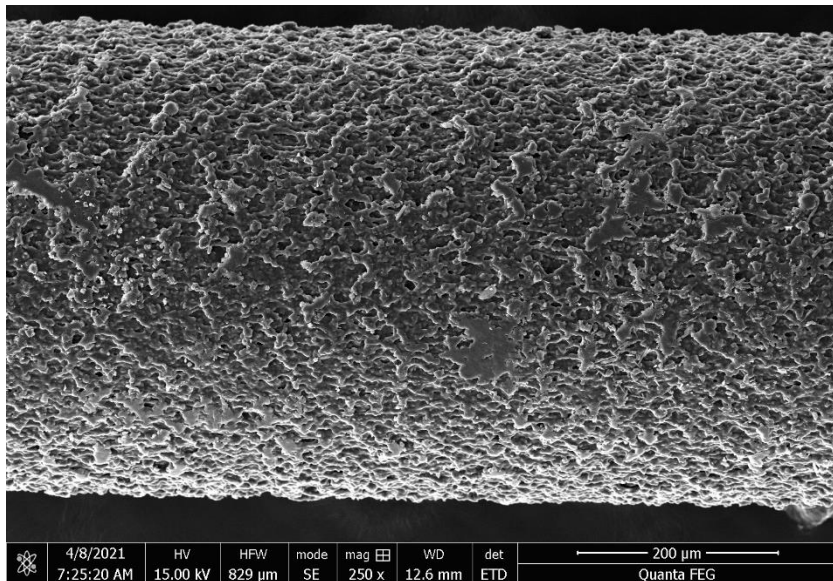
Steady State Diameter
 (n = 1474)



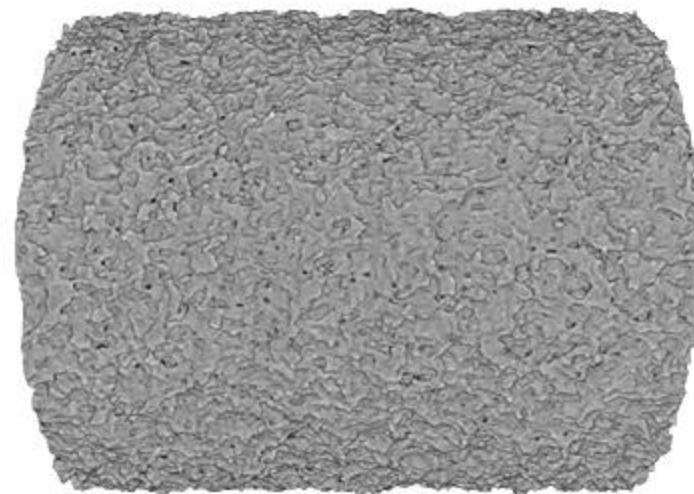
Structural analysis of DEX implant

SEM and MicroCT reveal irregular surface and 6% internal porosity

SEM profile



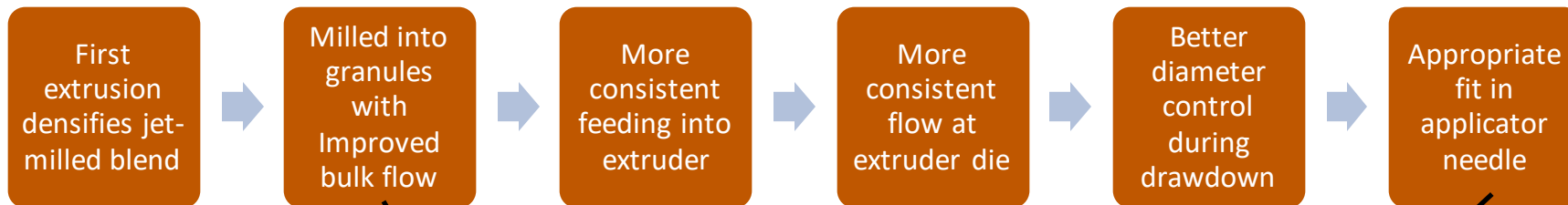
MicroCT profile



**MicroCT
Cross-section**

Internal voids
seen as dark spots

2-step extrusion process for implant structure control



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)**

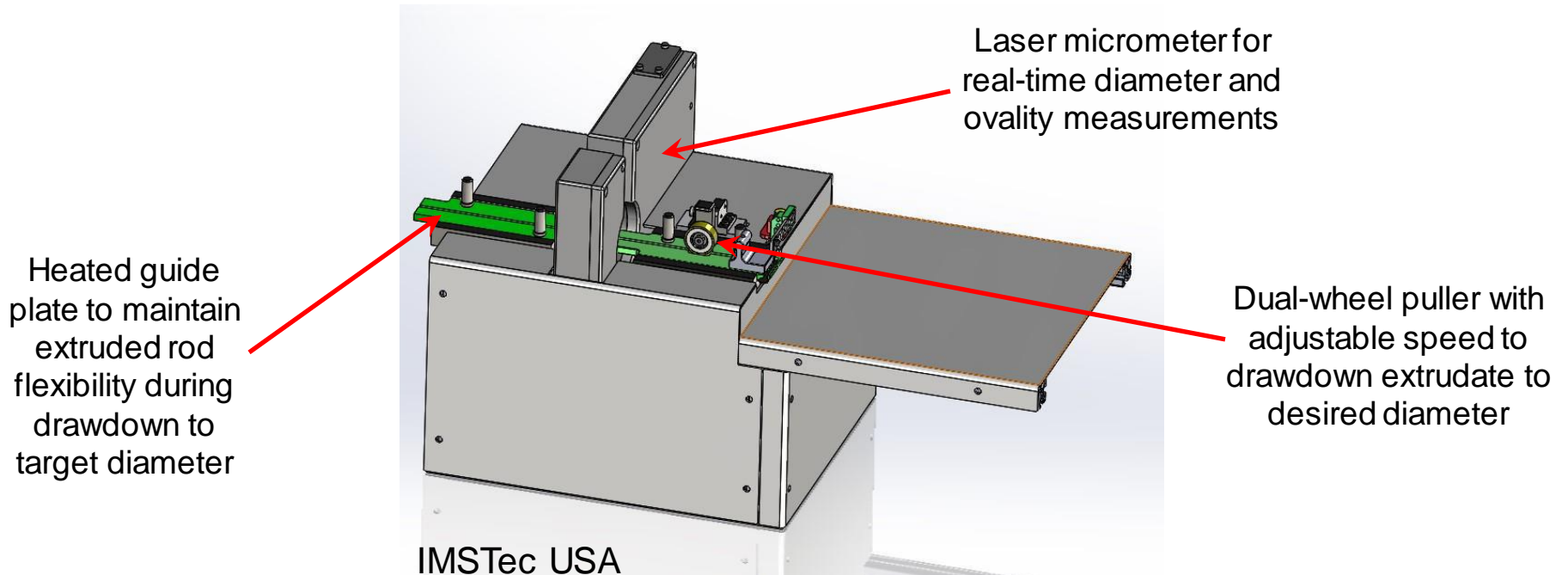
Stage 1: Brabender twin-screw volumetric feeder

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



Puller for controlled drawdown to target diameter

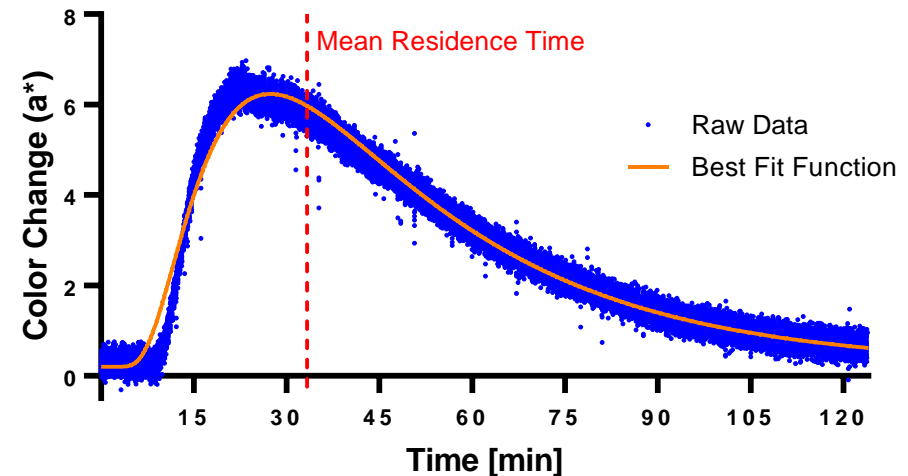
Purpose-built unit for fine adjustment of drawdown parameters



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

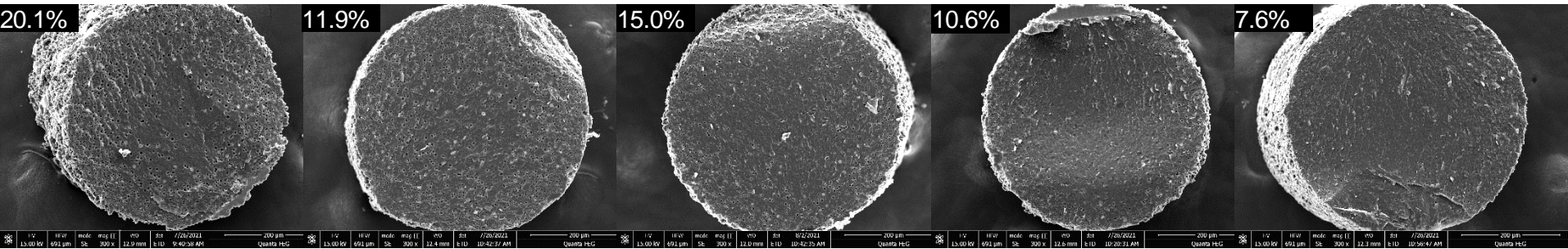
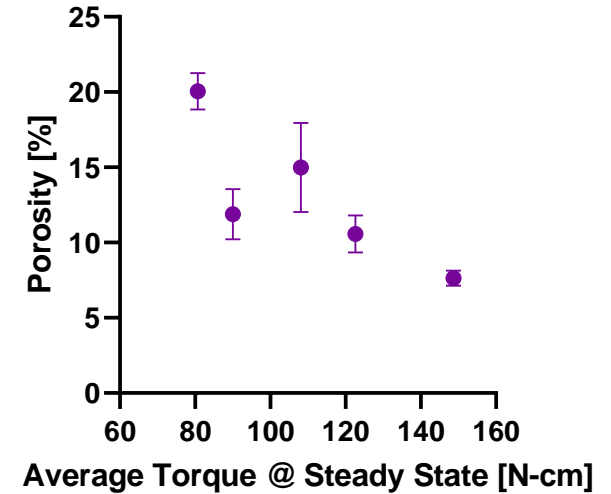
- Mean residence time = 33 min
 - Used tracer dye and laboratory camera to detect color change
 - In-house software developed for data acquisition and analysis
- Assay confirms DEX stability and uniformity
 - Potency: $100.1 \pm 0.2\%$ SD (N=6)
- GPC data shows 7% reduction in M_n

Residence Time Distribution Analysis
(Second Extrusion, N=94440)



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

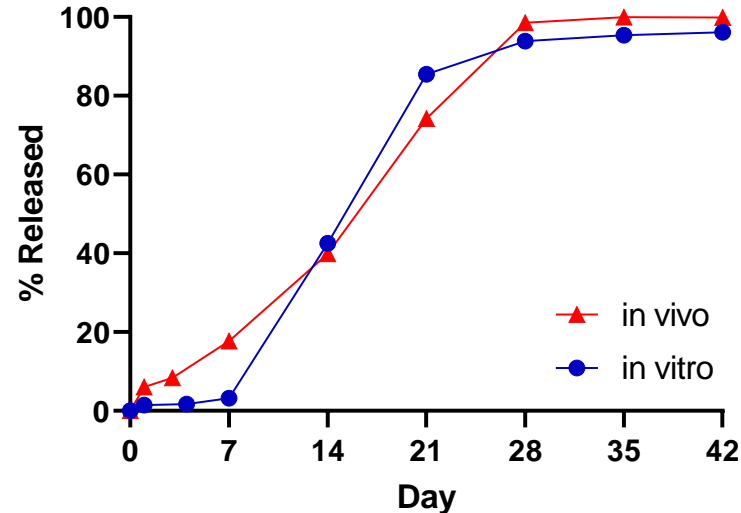
- Low glass transition temperature of PLGA enables the extrusion at relatively low temperature to maintain the chemical stabilities of dexamethasone
- Accurate diameter control was achieved with a two-step extrusion process using two-stage feeding design and a purpose-built downstream puller
- Various 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.**

in vitro / in vivo release from Ozurdex patent data



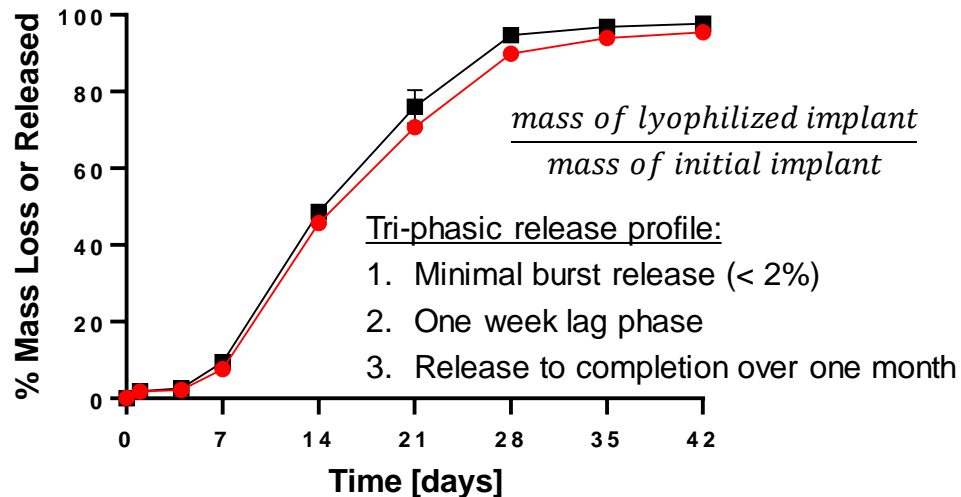
Replotted based on the data (Figs 2 and 10) in the patent

In vitro release testing in normal saline of DEX implants

Tri-phasic release profile aligns with published data

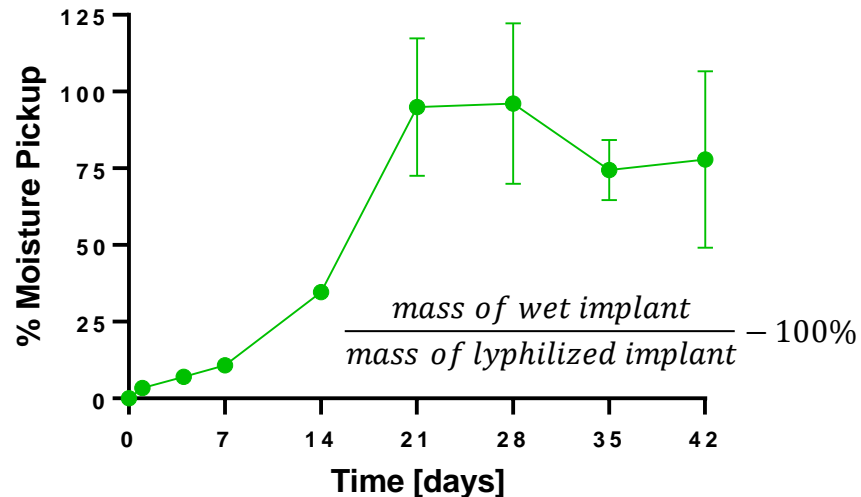
Dexamethasone Intravitreal Implant Dissolution

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.)

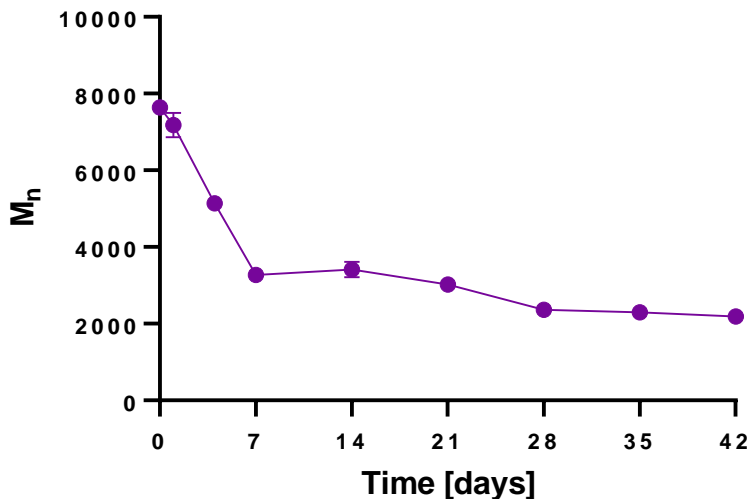


In vitro release testing in normal saline of DEX implants

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

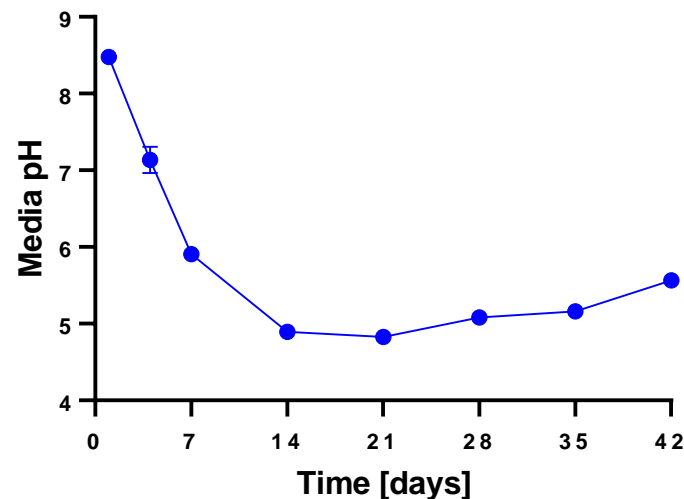
GPC - Change in PLGA Molecular Weight

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



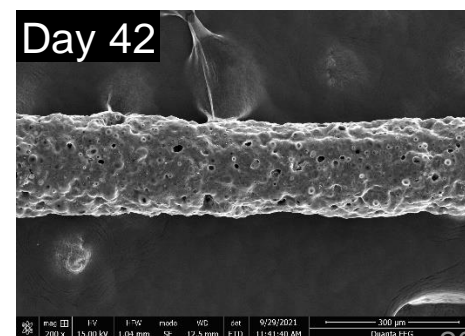
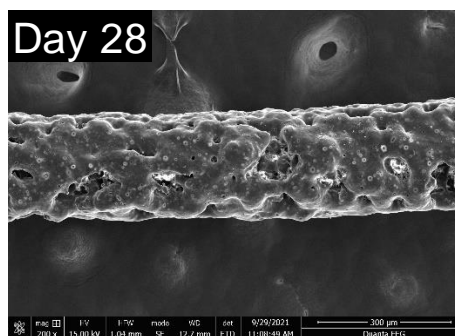
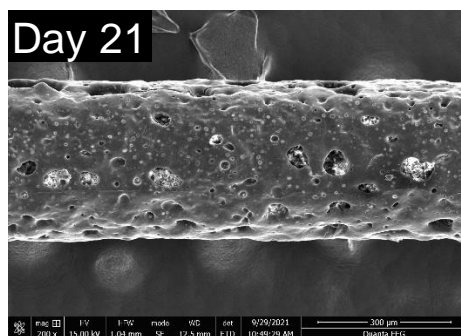
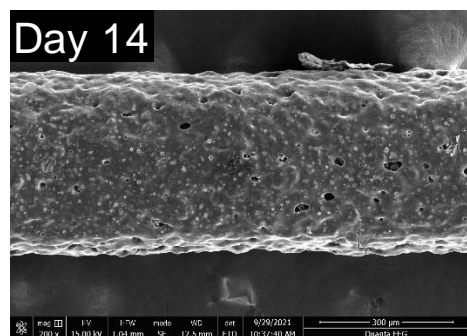
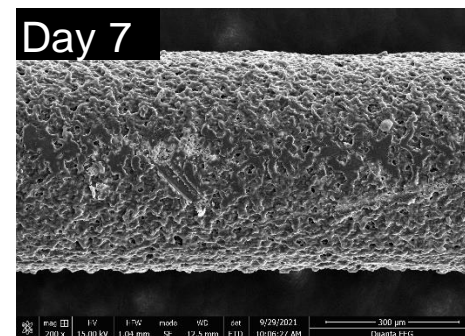
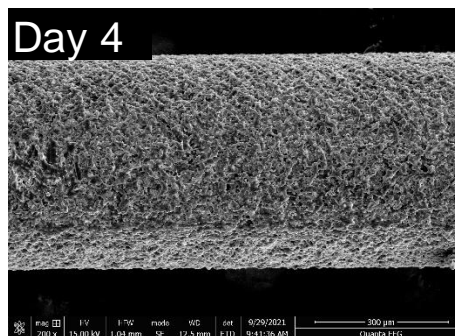
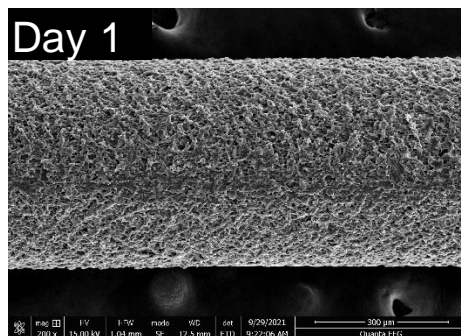
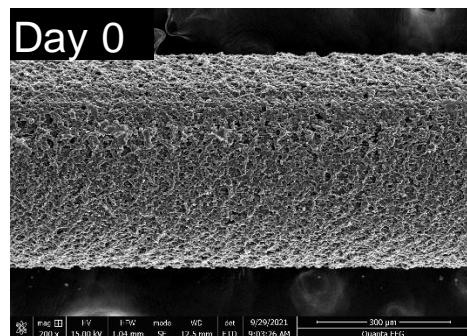
Change in Media pH

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



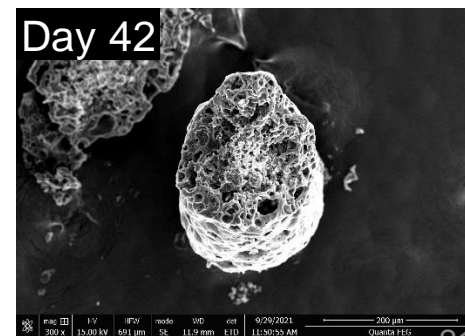
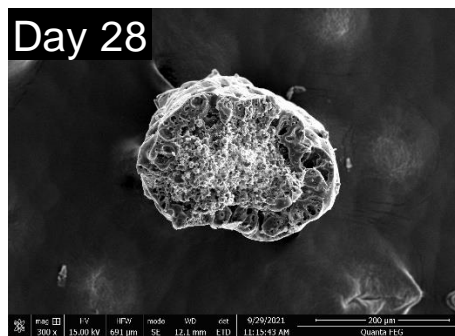
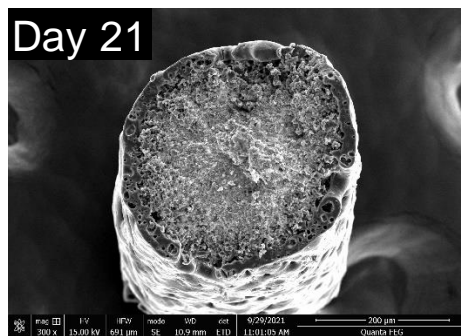
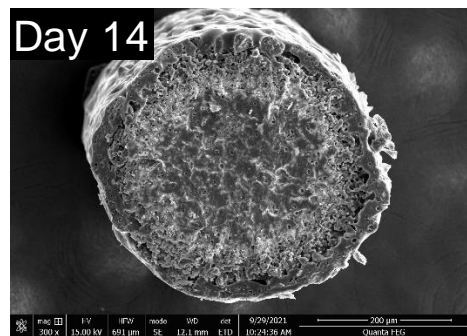
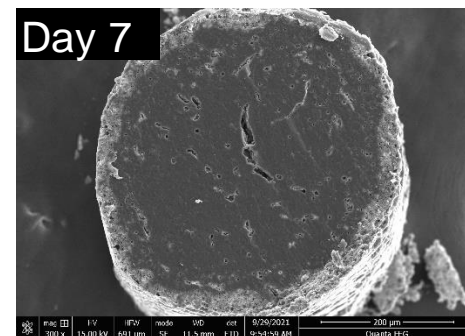
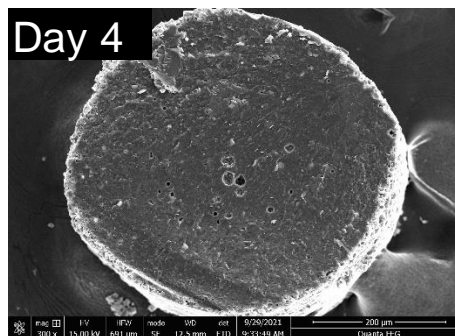
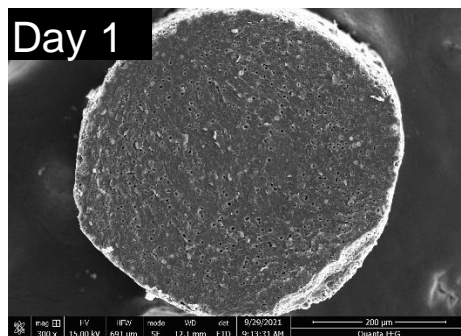
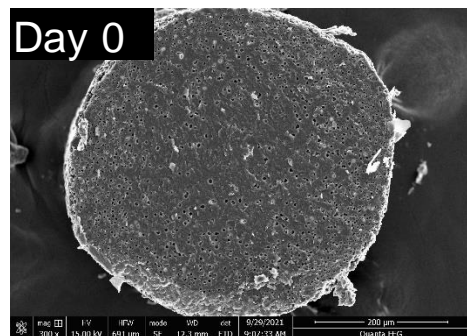
In vitro release testing in normal saline of DEX implants

SEM shows significant structural changes to implant after day 7



In vitro release testing in normal saline of DEX implants

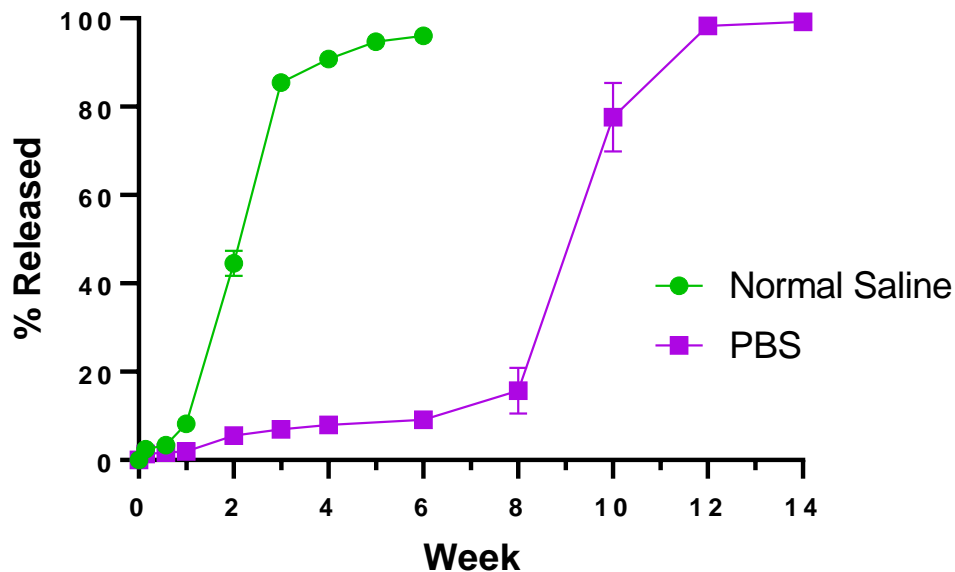
SEM shows significant structural changes to implant after day 7



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

Dexamethasone Intravitreal Implant Dissolution

37°C, 100 RPM, 30 mL, N=3



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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