Elastomeric and Biodegradable Hydralese™ (PGSU) Facilitates Novel Long-acting Oral Gastroretentive Devices and Injectable Microspheres

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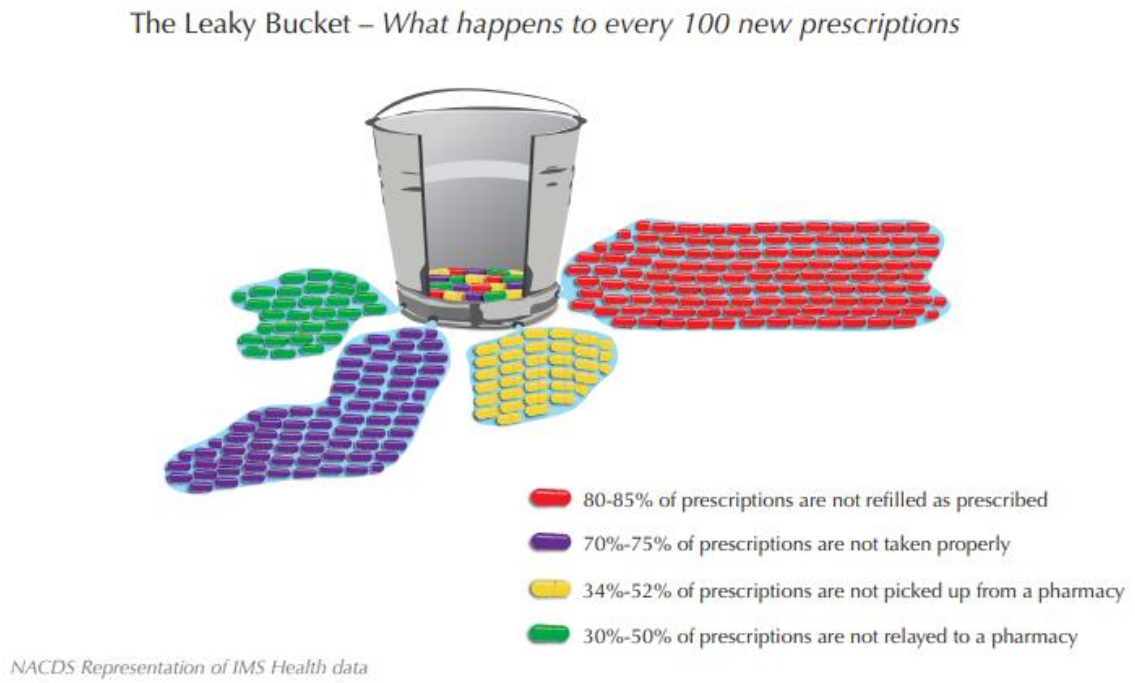
Advanced Delivery Science

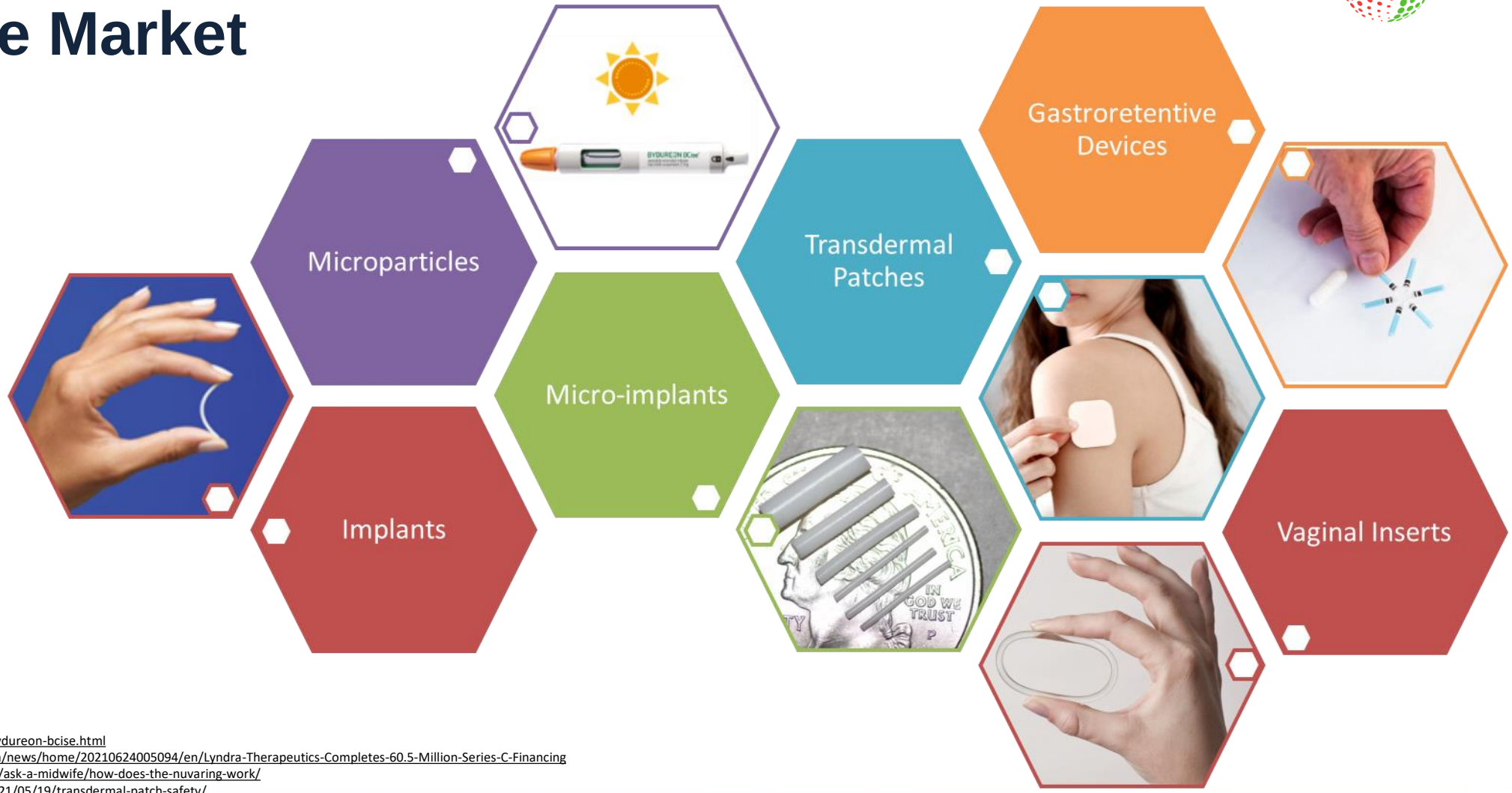
The Need for Long-acting Drug Delivery Systems (LADDS)



- Medications taken correctly help treat/manage chronic illnesses.
- However, non-adherence leads to not only poor health but also increased cost due to emergency room visits or extended hospital stays.
- Long-acting drug delivery systems improve patient compliance due to infrequent dosing.
- The active pharmaceutical ingredient (API) is available in the patient for a prolonged period of time, counteracting the elimination half-life.

Ref:
https://www.nacds.org/pdfs/pr/2011/PrinciplesOfHealthcare.pdf

Long-acting Drug Delivery Systems (LADDS) on the Market



Ref:
- https://www.nexplanon.com/
- https://www.bydureon.com/bydureon-bcise.html
- https://www.businesswire.com/news/home/20210624005094/en/Lyndra-Therapeutics-Completes-60.5-Million-Series-C-Financing
- http://ourmomentoftruth.com/ask-a-midwife/how-does-the-nuvaring-work/
- https://blog.uvahealth.com/2021/05/19/transdermal-patch-safety/

Overview of Presentation

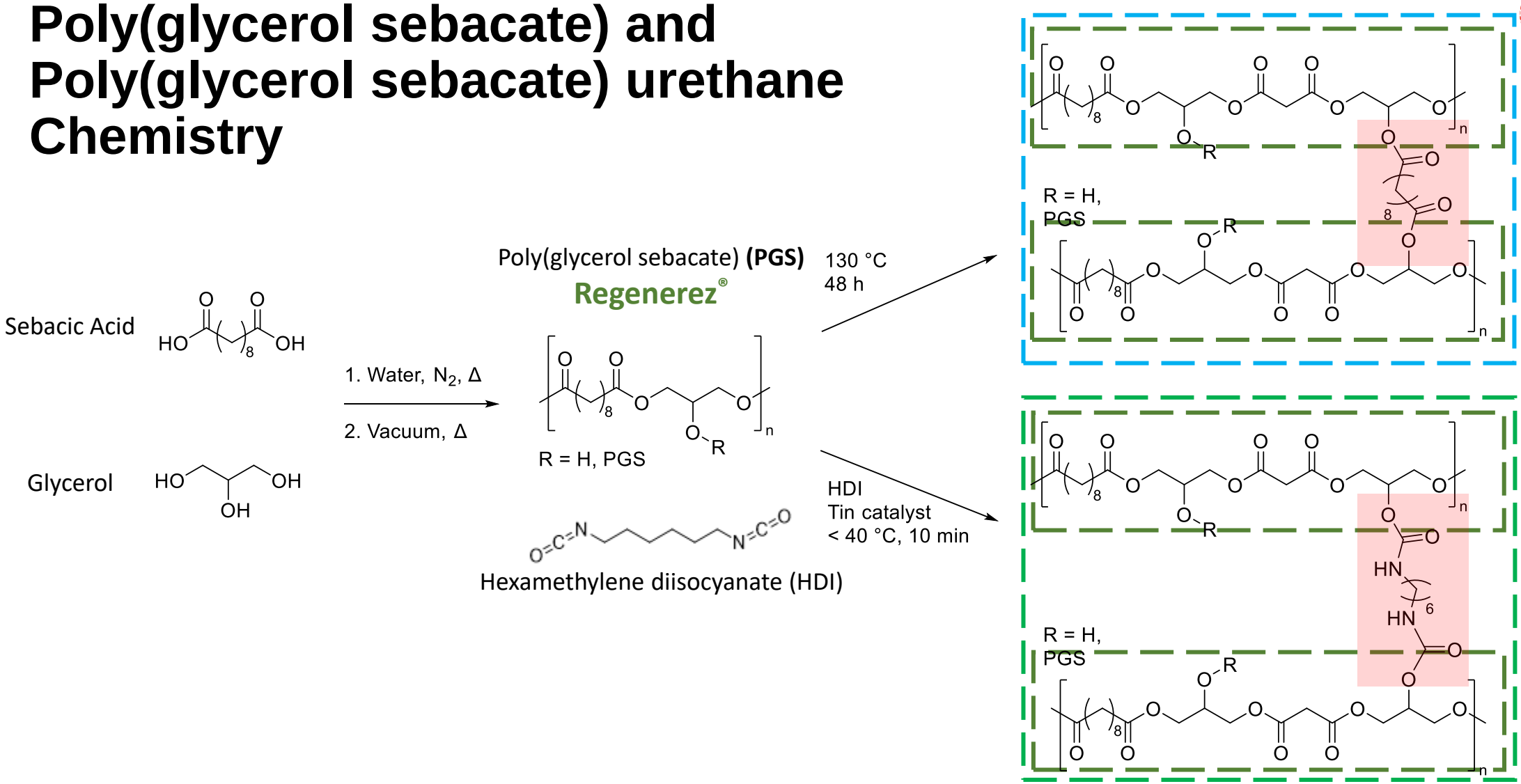
Secant Group's Hydralese™ (PGSU) platform for long-acting drug delivery

- ❑ PGS resin and PGSU chemistry
- ❑ Manufacturing of PGSU devices
- ❑ Comparison of PGSU to other polymers in LADDS
- ❑ Hydralese development

Hydralese™ (PGSU) based devices

- ❑ Gastroretentive devices
  - ✓ Manufacturing process and optimization of shapes
  - ✓ *In vitro* release in simulated gastric fluid (SGF)
  - ✓ *In vivo* studies in domestic swine and beagle dogs
- ❑ Microspheres
  - ✓ Manufacturing processes
  - ✓ Formulation of microspheres suspension
  - ✓ *In vitro* release

Poly(glycerol sebacate) and Poly(glycerol sebacate) urethane Chemistry



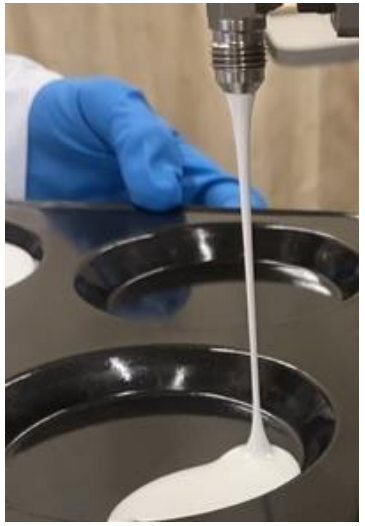
Manufacturing Hydralese (PGSU) Dosage Forms

+

API powder dispersed into liquid PGS resin
Commonly using a speed mixer

Crosslinker HDI

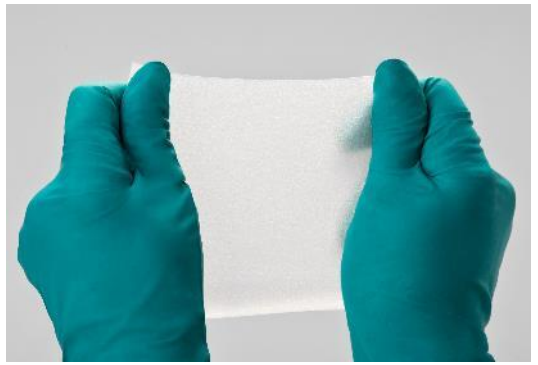
<40 °C

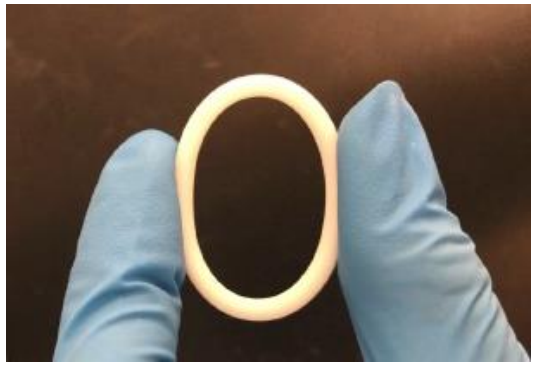


Blend dispensed into mold

Curing

RT
10 min





Drug-loaded elastomer removed from mold after 24 hours

Hydralese Tunable Platform

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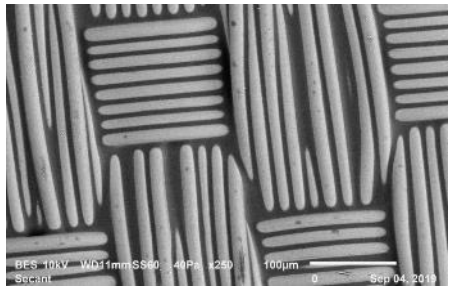
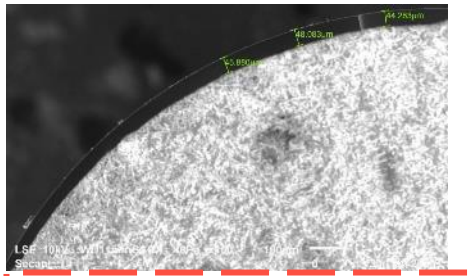
Rod Implants

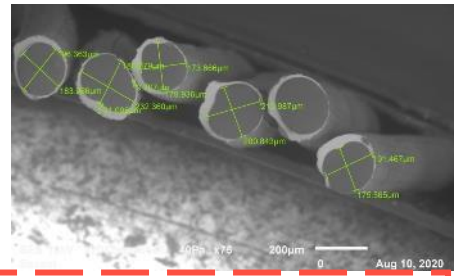
Textile Coatings



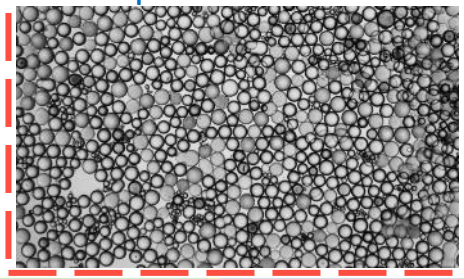
Core-sheath Implants



Fibers



Microspheres



Gastroretention

PGS Resin → **Crosslinking** → **PGSU Elastomer**

Attributes	Hydralese ™ (PGSU) Specifications
Elasticity (tensile)	20-100% strain, 4-12 MPa modulus
Degradation timeframe	3-18 months
Degradation mechanism	Hydrolysis
Permeability	Water impermeable
Anti-adhesion	Yes
Regenerative	Yes
Biocompatibility	No inflammation, no fibrosis
Crosslinking	3-10 min @ 23°C
Manufacturing process	Extruding, molding, casting, coating, 3D printing, emulsion
Storage	Room temperature, room humidity

X-ray Microscopy Imaging of 2’-deoxyadenosine loaded PGSU Rods

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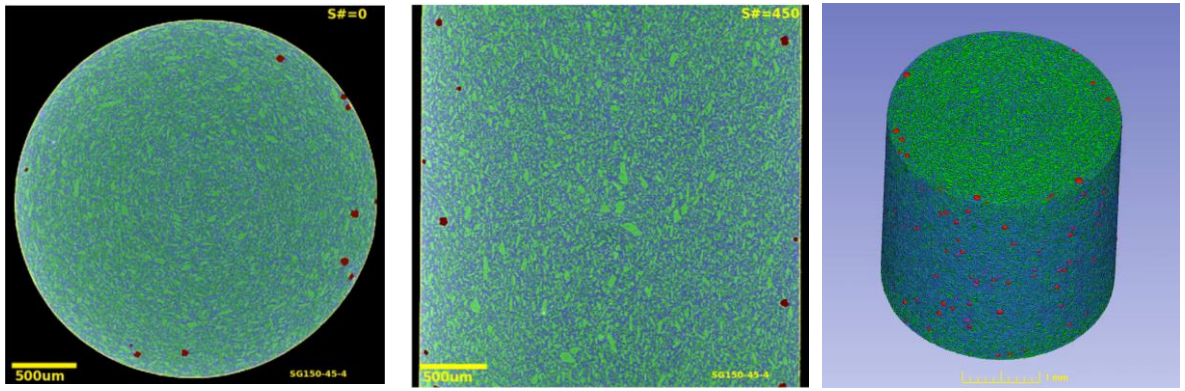
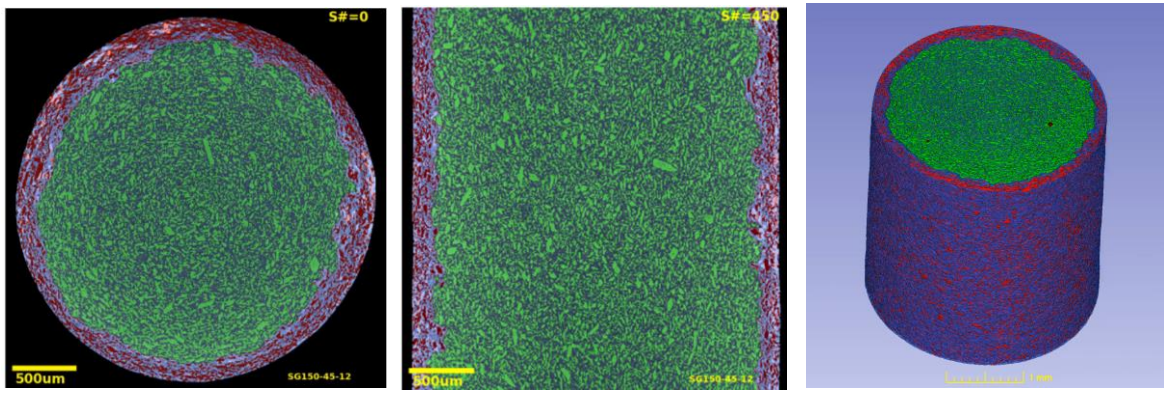
Pre-existing Pore | API | Polymer

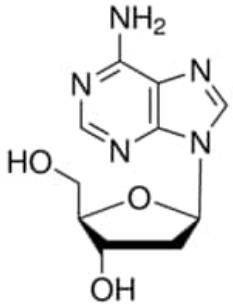
Outer Post-release Pore | Pre-existing Pore | API | Polymer

Pre-release



Post-release





2’-deoxyadenosine

	Pre-release	Post-release	
		Outside Layer	Inside Layer
Porosity (% v/v)	0.30	39.82	0.01
Drug (% v/v)	43.00	0.0	44.04
Polymer (% v/v)	56.70	60.18	55.95

- XRM shows uniform distribution of API in PGSU matrix.
- Porosity of the outer layer where drug has released correlates to original loaded drug volume.

Ref:
https://www.sigmaaldrich.com/deepweb/content/dam/sigma-aldrich/structure5/194/mfcd00005754.eps/_jcr_content/renditions/mfcd00005754-medium.png

Commonly Used Polymers in LADDS

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		Biodegradables			Biodurables		
Category	Feature	PGSU	PLGA	PCL	EVA	TPU	PDMS
Drug Delivery	Therapeutic duration >6 months	✓		✓	✓	✓	✓
	High drug loading >50% w/w	✓					
	Zero-order release kinetics	✓					
	Degradable once payload released	✓					
	Reduced burst effect once implanted	✓					
	Reduced tail effect once sub-therapeutic	✓					
	Minimal pH change during implant lifespan	✓		✓	✓	✓	✓
Patient Focus	Minimal fibrous encapsulation	✓		✓	✓	✓	
	All tissues return to normal post treatment	✓			✓	✓	
	Flexible, even at high loading for patient comfort	✓				✓	✓
	Discrete	✓				✓	✓
	Retrievable initially if adverse reaction	✓			✓	✓	✓
	No need for implant retrieval after therapy	✓	✓	✓			
	No chronic inflammatory response	✓			✓	✓	
	Provides patient convenience with reduced dosing	✓			✓	✓	✓
Stability	Polymer stable under sterilization	✓			✓	✓	✓
	Room temp/humidity shelf storage	✓			✓	✓	✓

Evolution of Hydralese (PGSU)

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2015
- ✓Secant Group develops Regenerez®
- ✓Secant Group develops a proprietary process for commercial scale-up of PGS resin

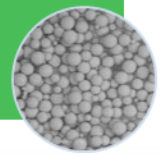
2016
- ✓Secant Group establishes collaborations with academia in large animal models
- ✓Secant Group develops cardiovascular grafts

2017
- ✓Expansion of PGS in regenerative tissue engineering applications

2018
- ✓Hydralese is developed for controlled release
- ✓Collaborations on pharma projects begin
- ✓Subcutaneous implants developed

2019
- ✓Small molecule formulations are developed
- ✓Sustained release from 3-12 months observed
- ✓Long-term animal studies conducted; studies show biocompatibility

2020
- ✓Expansion of device form: microspheres, gastroretentive devices
- ✓Continued collaborations with pharma

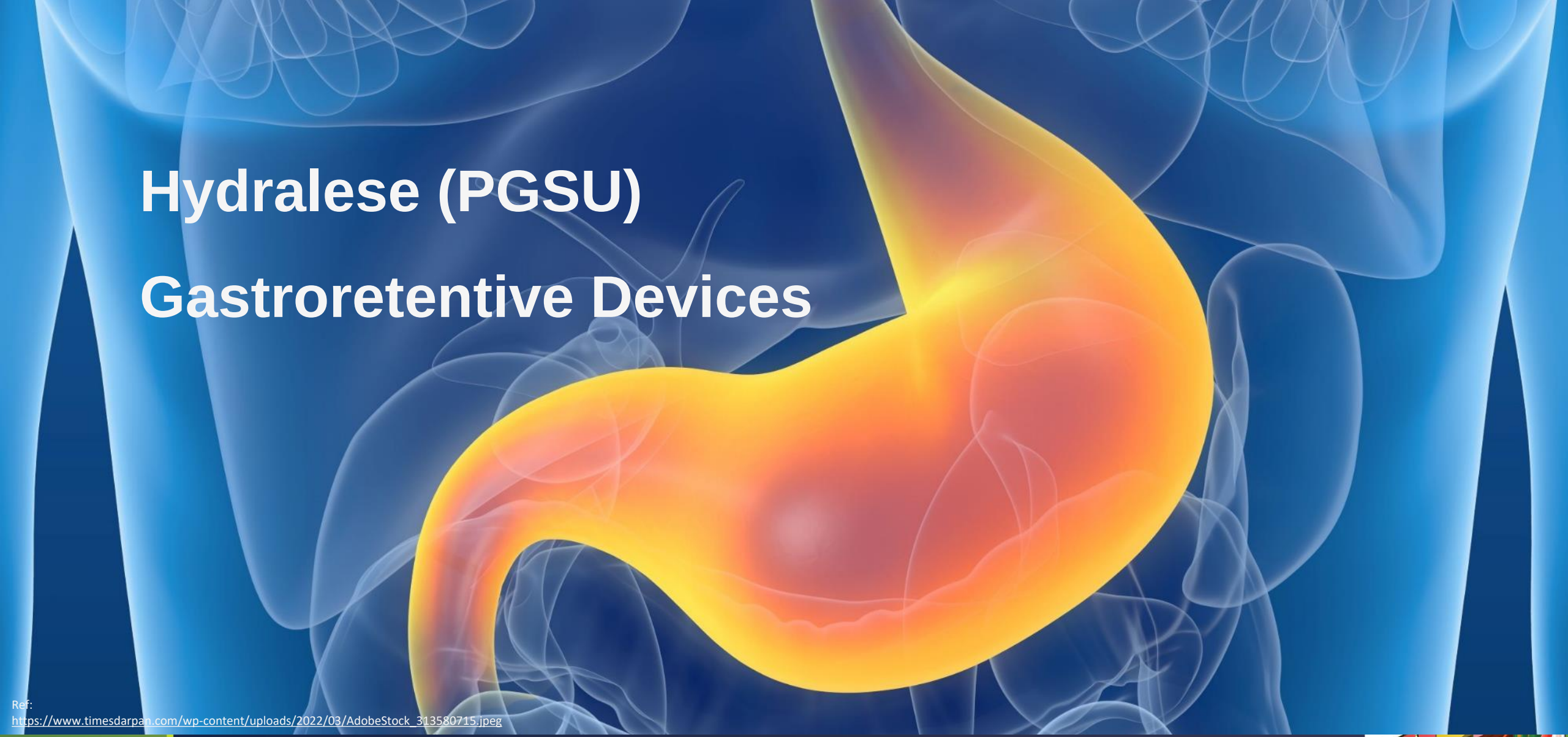


2021
- ✓PGSU controlled release patent issued
- ✓DMF filed with the FDA
- ✓Expansion of device form: micro-scale implants
- ✓MPT (multi-purpose prevention therapy) and ocular therapy

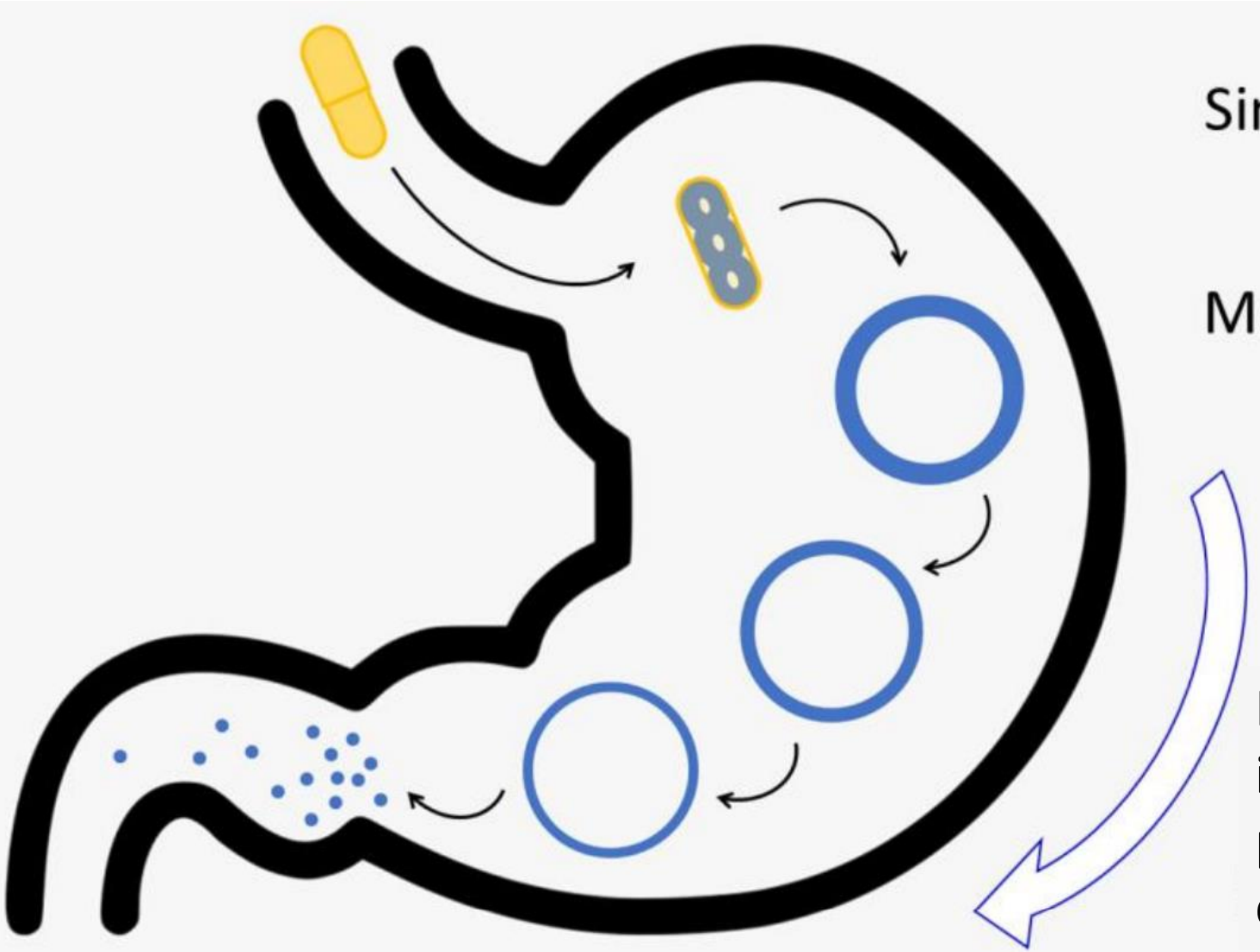
2022
- ✓Expansion into large molecule delivery
- ✓Continued collaborations with pharma on gastroretention, ocular implants, microspheres, and subcutaneous implants

Hydralese (PGSU)

Gastroretentive Devices



Ref:
https://www.timesdarpan.com/wp-content/uploads/2022/03/AdobeStock_313580715.jpeg

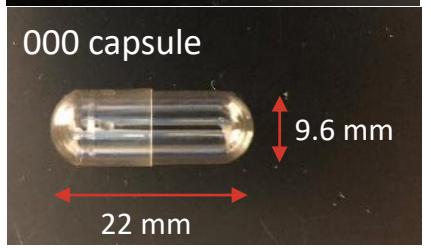


Single-Component PGSU + API

Molded Geometry

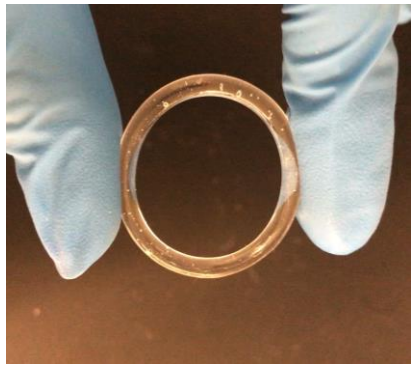
Loss of mechanical integrity after a period of time - device eliminated

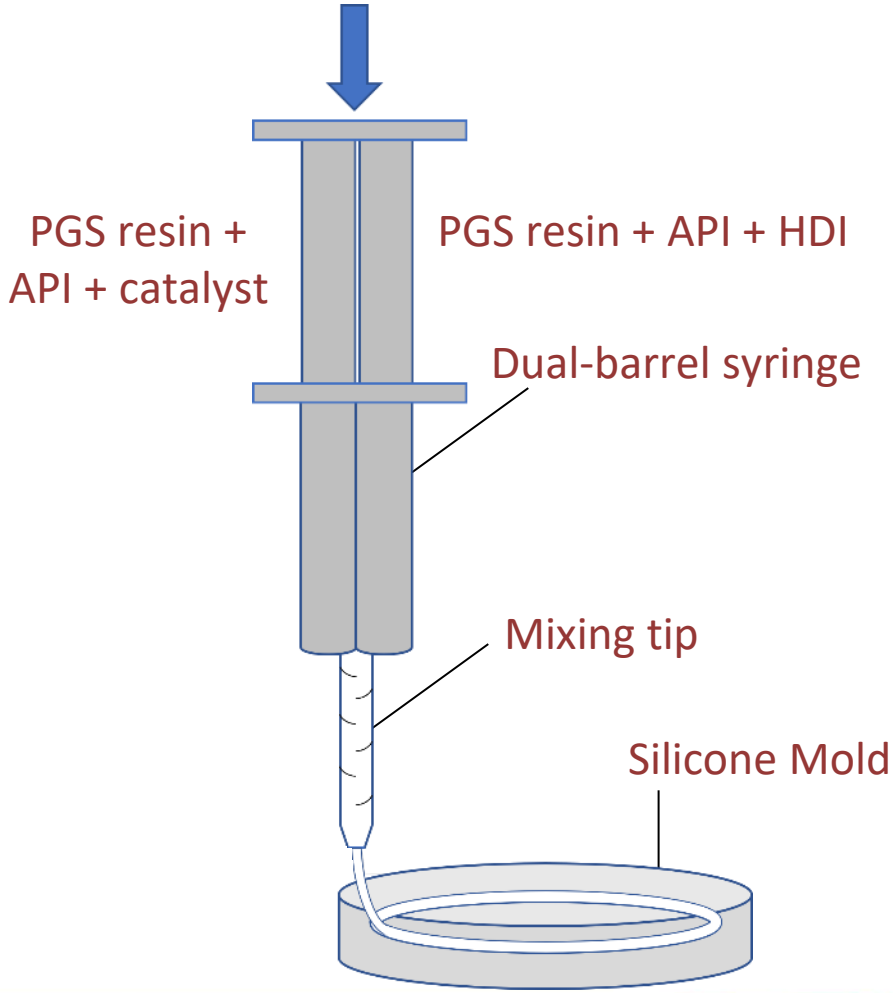
The device must…
- ✓Compress to fit inside a 000 capsule
- ✓Spring back to its original shape
- ✓Remain in the stomach for a defined length of time
- ✓Sustain therapeutic release in an API for a desired period of time



Manufacturing PGSU Gastroretentive Devices

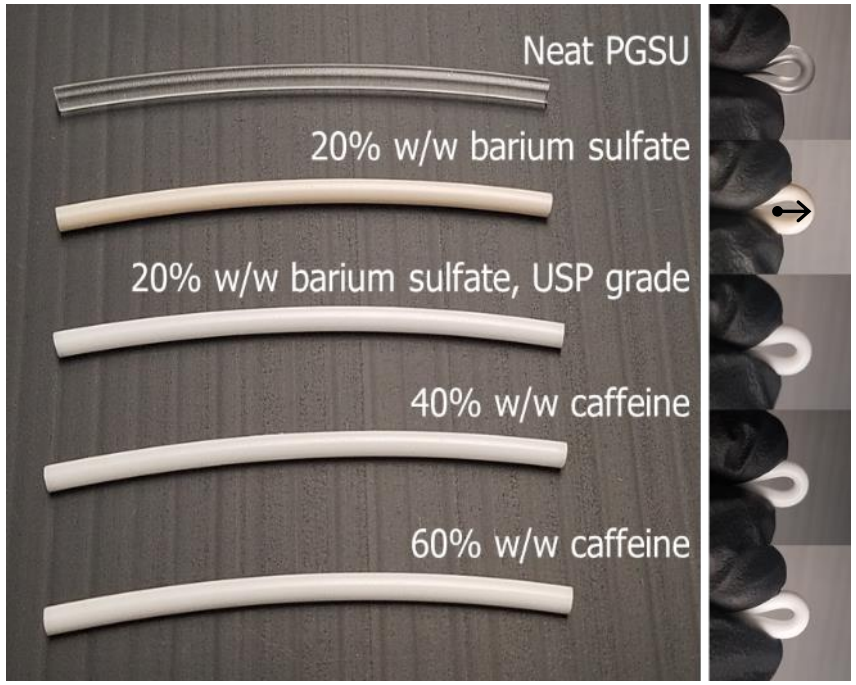
Component	Concentration	mg/Device
PGSU	40-100%	
API	Up to 60%	Up to 600

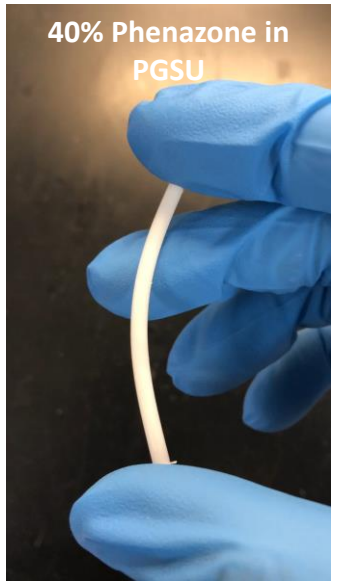



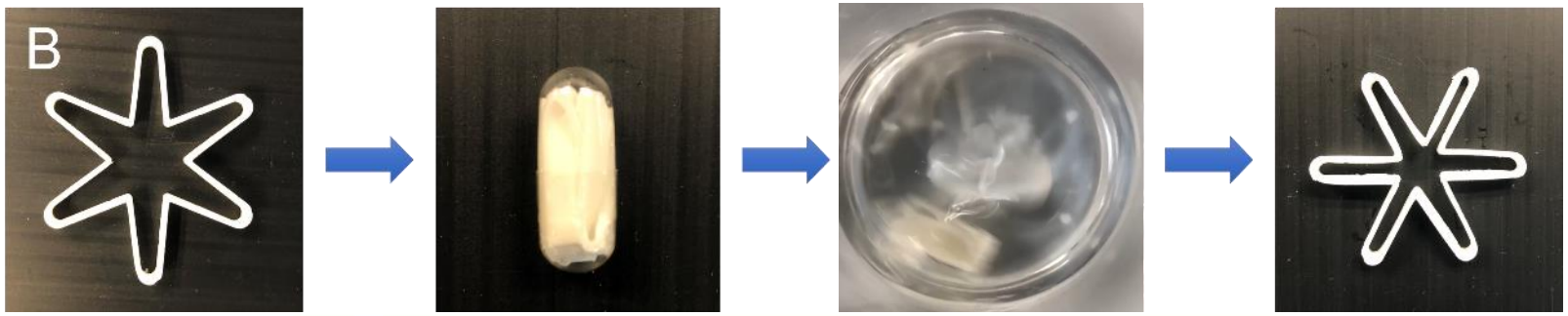


Factors Affecting Device Flexibility

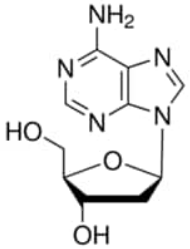
1. **Particle Size**
   - Micronized API gives a smaller bend radius than larger particles.
2. **%API Loading**
   - Increasing loading can decrease flexibility.
3. **Shape**
   - Cross-sectional dimensions
   - Foldable sections
4. **Degree of solvation**
5. **Crosslinking**







Factors Affecting Device Release Kinetics

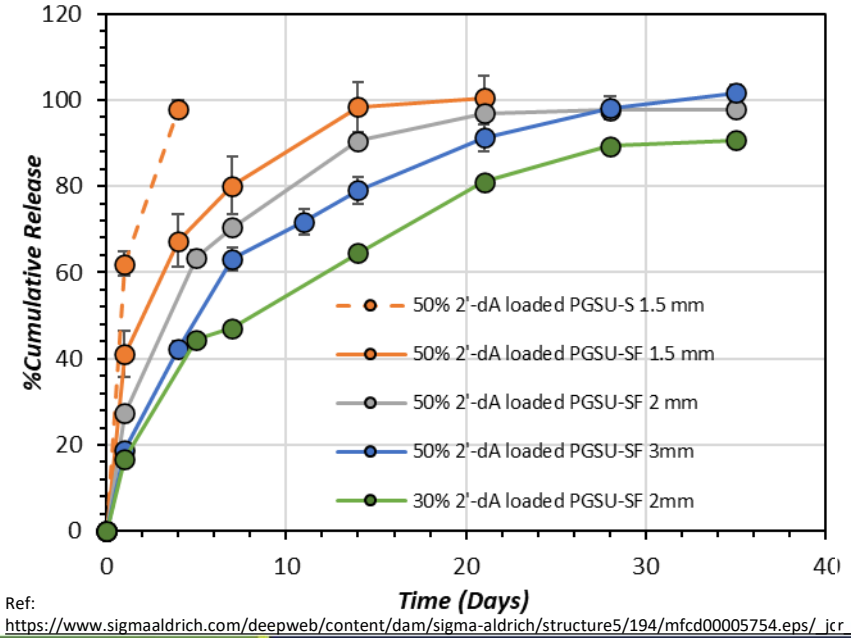


2'-deoxyadenosine (2'-dA): model water soluble API (25 mg/mL)

Factors affecting *in vitro* release	Factors that DO NOT affect *in vitro* release
Device diameter	API particle size
%Drug loading	pH of SGF
Solvation	Rabbit Gastric lipase (RGL)

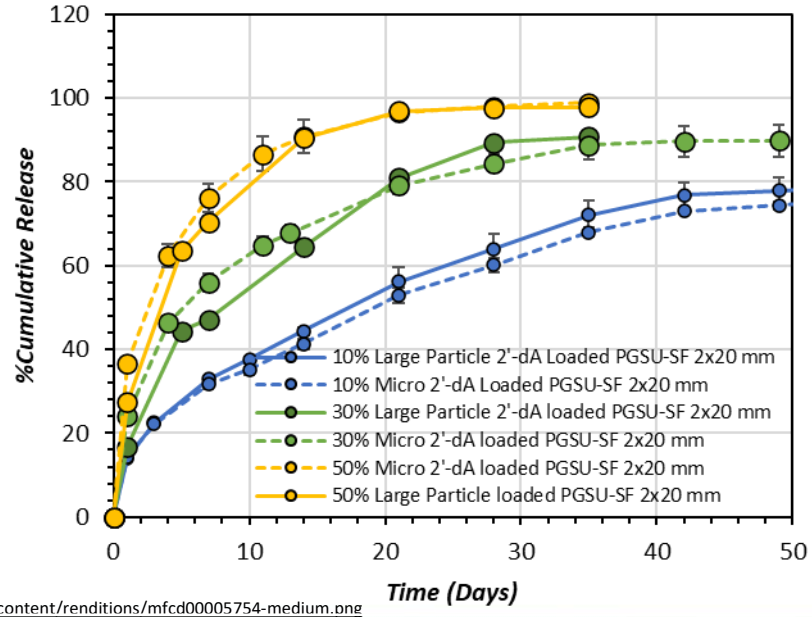
Studies carried out *in vitro* in simulated gastric fluid (SGF) at pH 1.2 and 37°C

Solvated devices release faster than solvent-free devices. Devices with smaller diameter release faster.

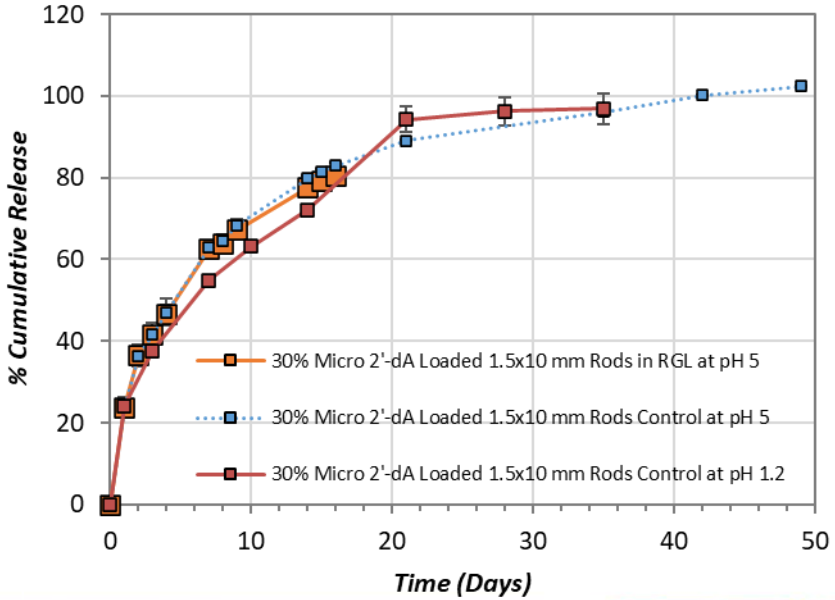


Ref: https://www.sigmaaldrich.com/deepweb/content/dam/sigma-aldrich/structure5/194/mfcd00005754.eps/_jcr_content/renditions/mfcd00005754-medium.png

Higher %DL shows faster release *in vitro.* API particle size has no effect on release.



Rabbit gastric lipase (RGL) and change in pH have no effect on release.



In vivo Studies in Domestic Swine: Formulation Details

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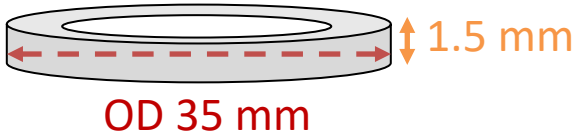
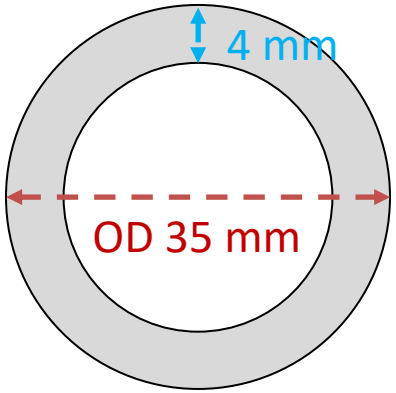
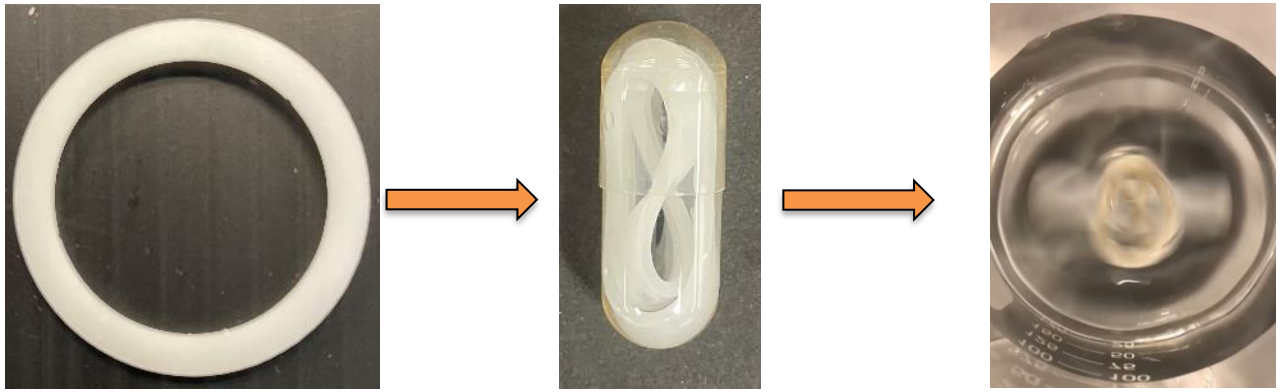
Placebo Rings in Domestic Swine



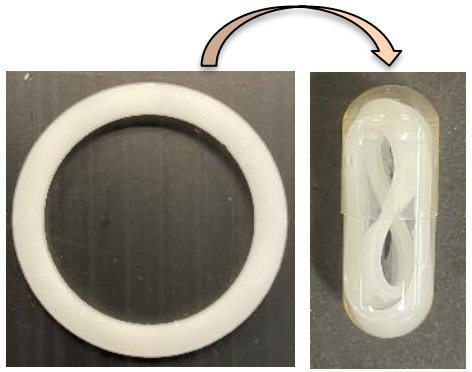


3 total:
2 swine: one 5% $BaSO_4$ ring each
1 swine: one unloaded ring

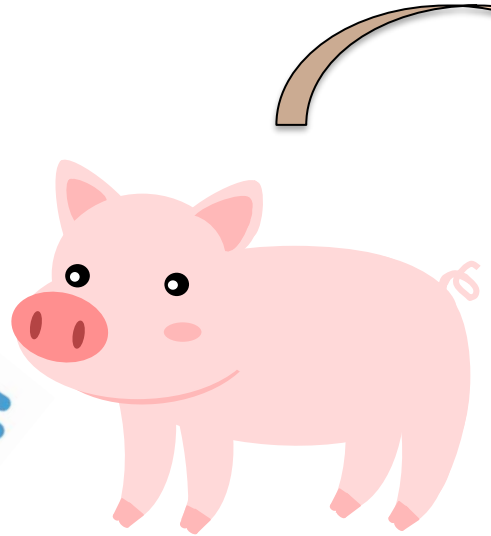


In vivo Studies in Domestic Swine: Study Protocol

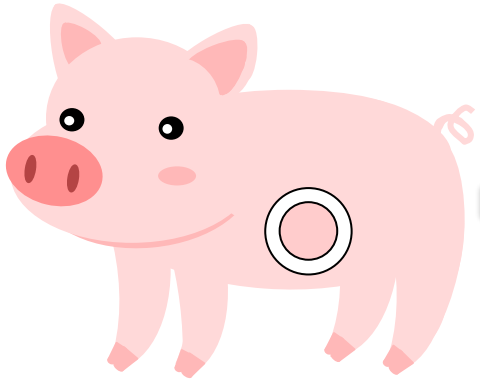
Placebo ring was placed into a 000 capsule.

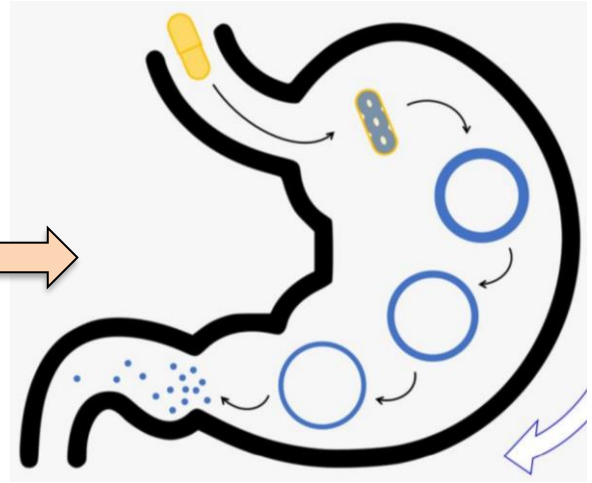


Three domestic swine were dosed orally with one ring each.



The capsule dissolved and the PGSU ring sprung to its original shape.

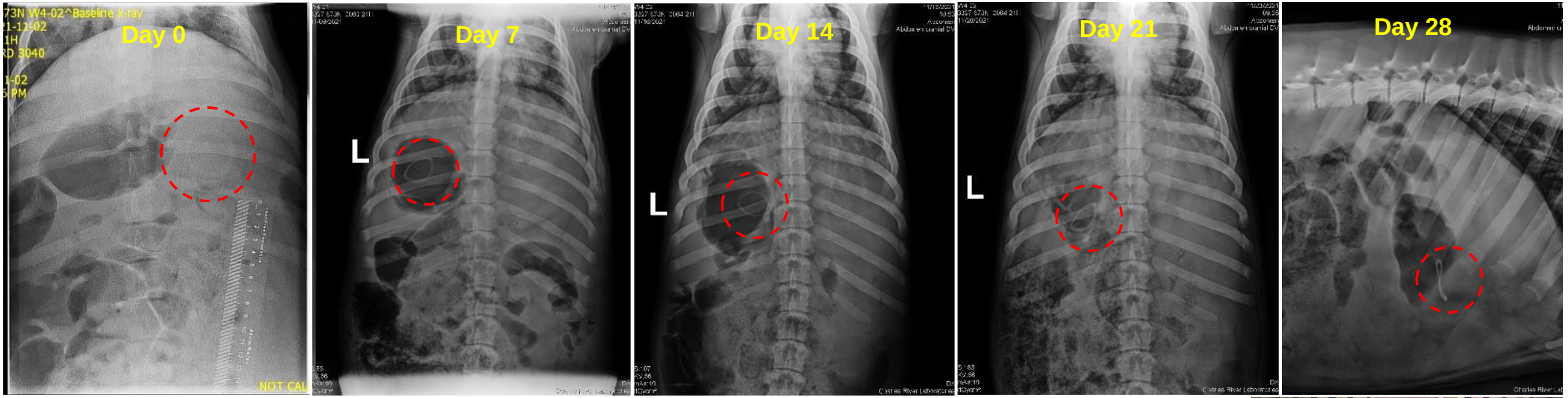


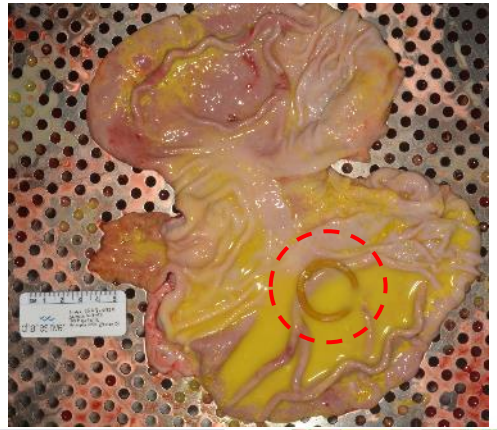


Animals were observed for 28 days.

- Weekly X-ray
- Daily stool and vomitus catch

In vivo Studies in Domestic Swine: X-ray Imaging





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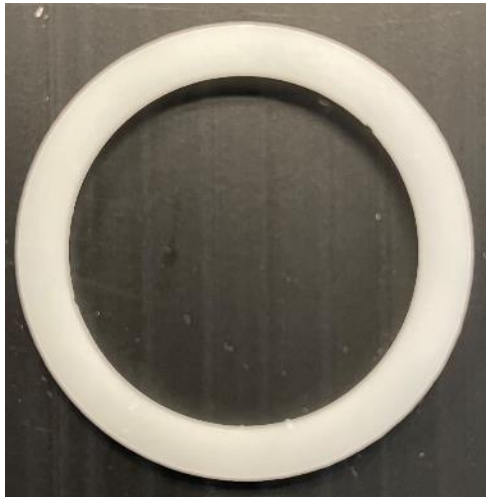
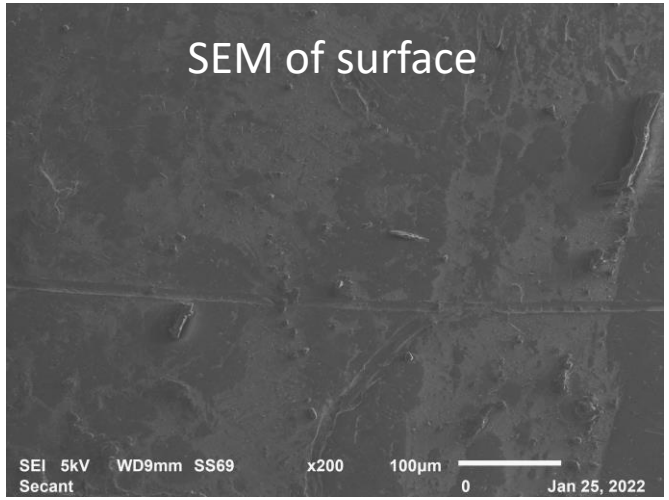
The gross pathology revealed no notable or dramatic findings related to safety and tolerability of rings.

In vivo Studies in Domestic Swine: Explant Analysis

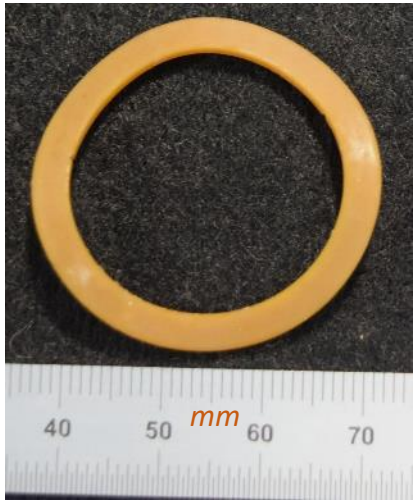
Gastroretentive Device	Time in vivo (days)	Width loss (%)	Thickness loss (%)
Placebo rings (5% $BaSO_4$) – 1.5x4x35 mm	28	5.11 ± 2.36	6.71 ± 1.37

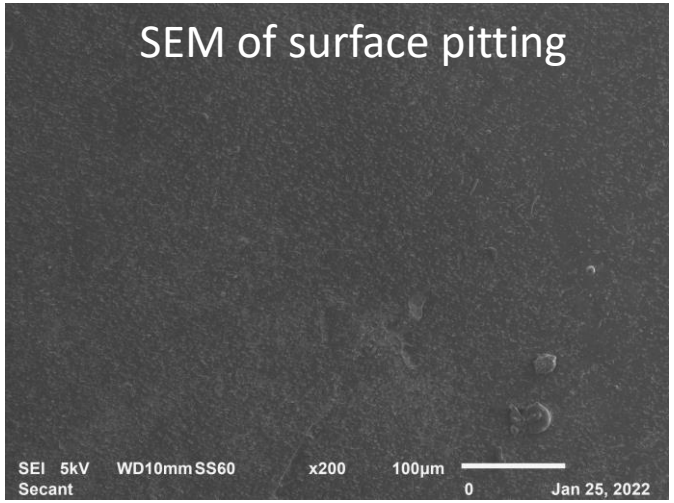
Pre-ingestion





Post-ingestion





Ring obtained from swine stomach post study (28 days)

In vivo Studies in Beagle Dogs: Formulation Details

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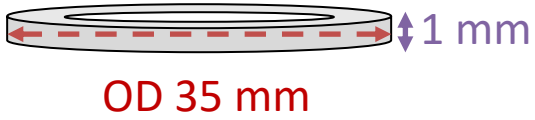
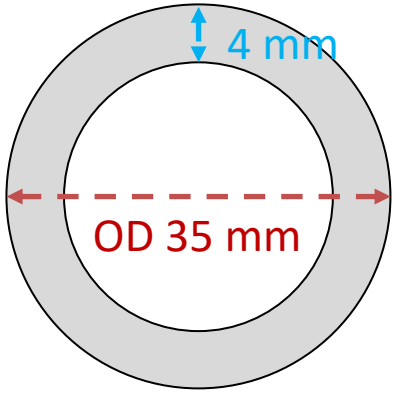
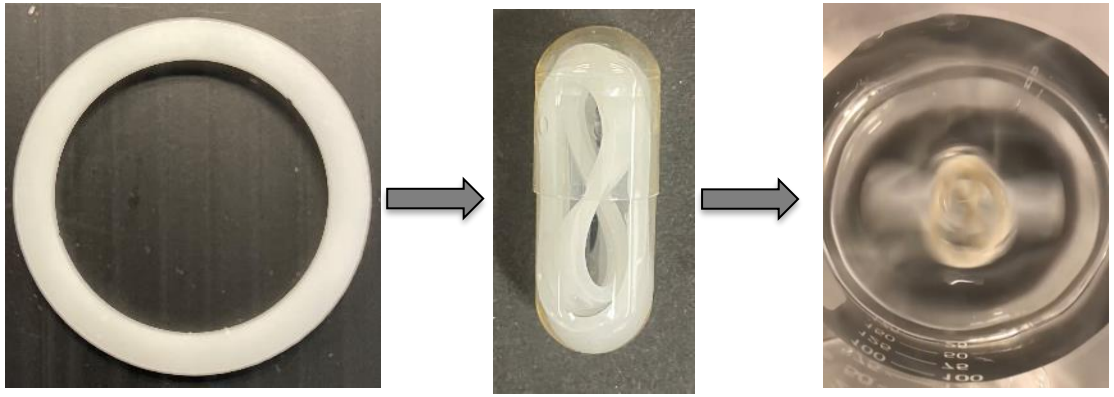
30% Dexamethasone (Dex)-loaded with 5% $BaSO_4$ Rings in Beagle Dogs

Each ring weighed 500 mg
150 mg Dexamethasone/Ring





5 Total
3 dogs: 1 ring each
2 dogs: 3 rings each



In vivo Studies in Beagle Dogs: Study Protocol

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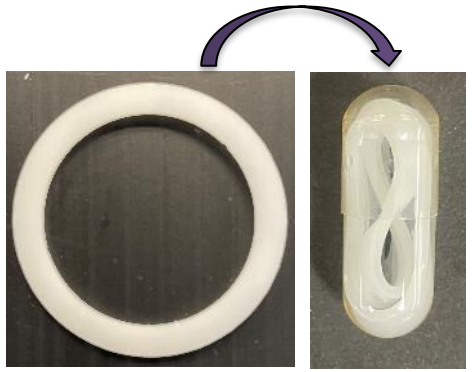
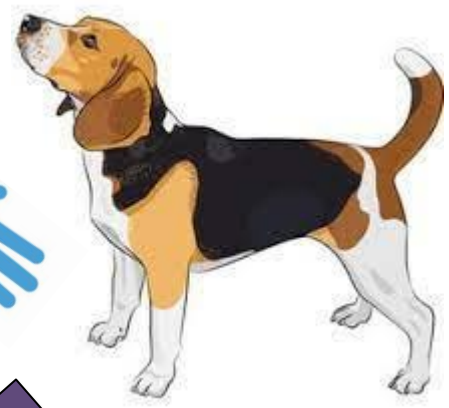
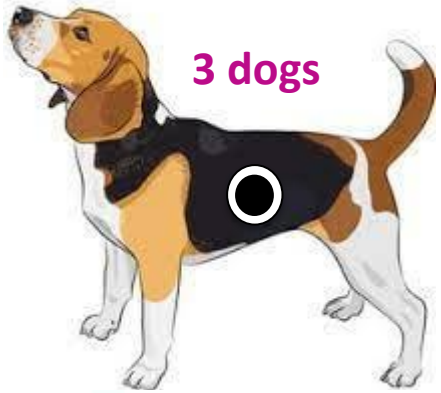
Dex-loaded ring was placed into a 000 capsule.

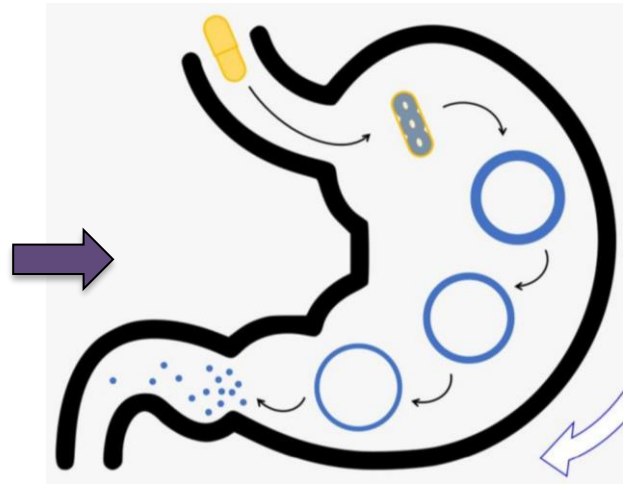




Beagle dogs were dosed orally.

The capsule dissolved and PGSU ring sprang to its original shape.



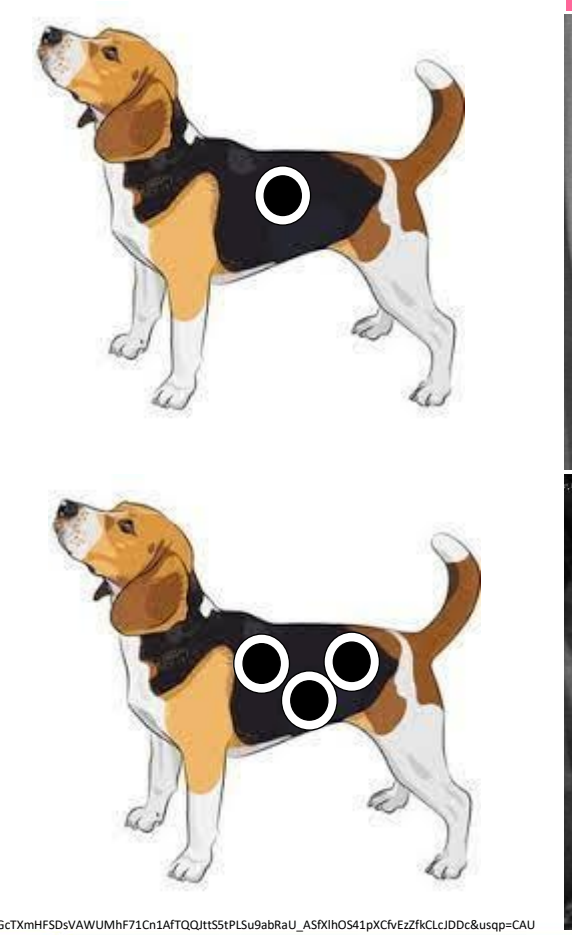
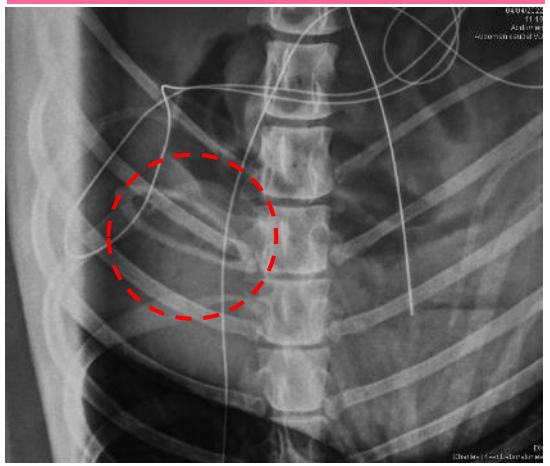
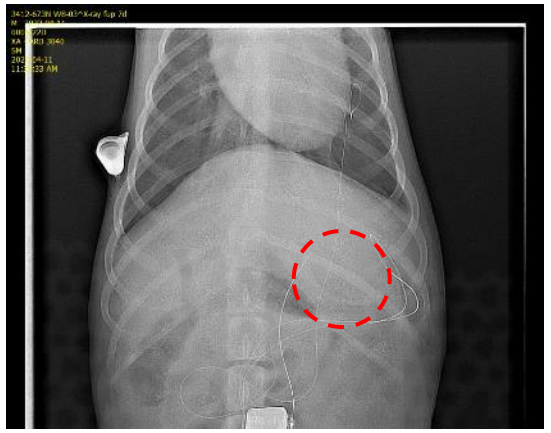
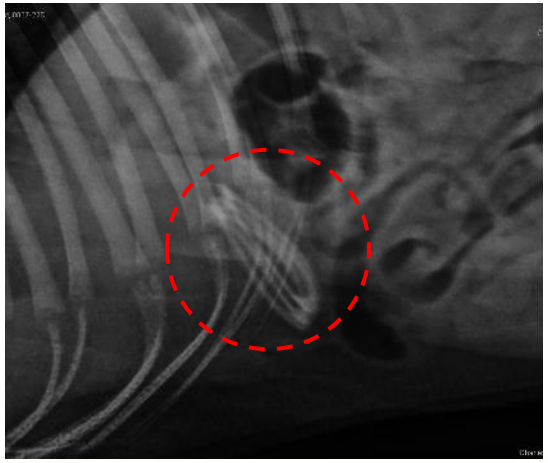
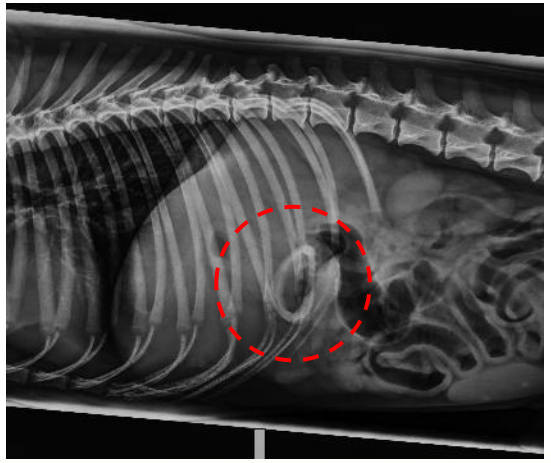


- Weekly X-ray
- Daily stool and vomitus catch
- Weekly blood draw

Ref:
https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcTXmHFSDsVAWUMhF71Cn1AfTQQJttS5tPLSu9abRaU_ASfXlhOS41pXCfvEzZfkCLcJDDc&usqp=CAU

In vivo Studies in Beagle Dogs: X-ray Imaging

secant group
charles river

	Day 0	Day 7	Day 14
1 Ring			
3 Rings			

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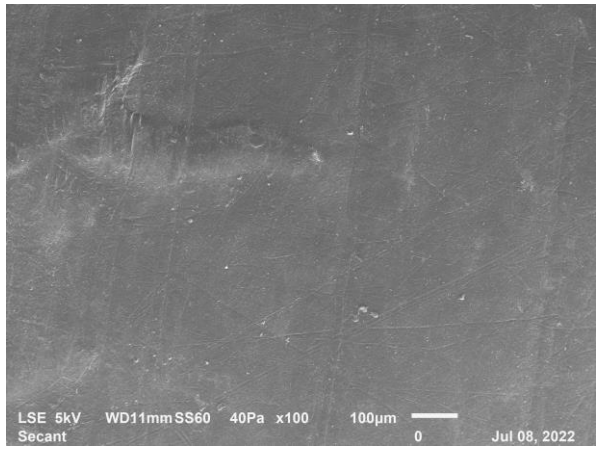
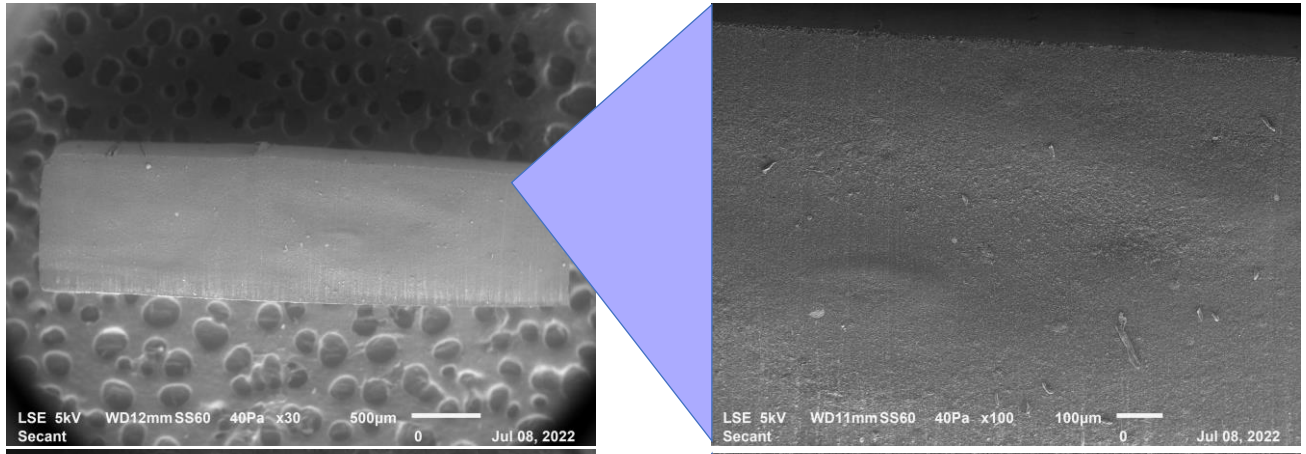
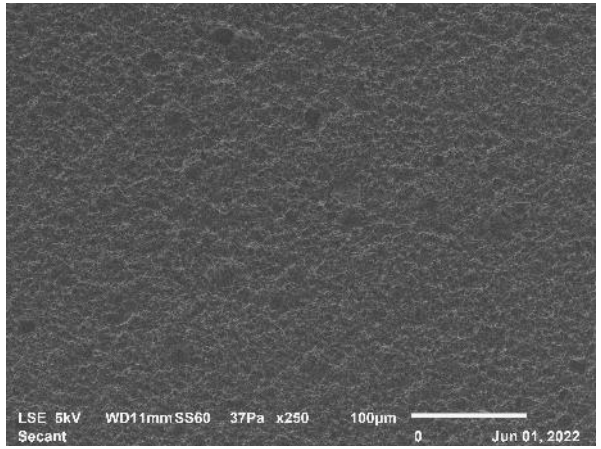
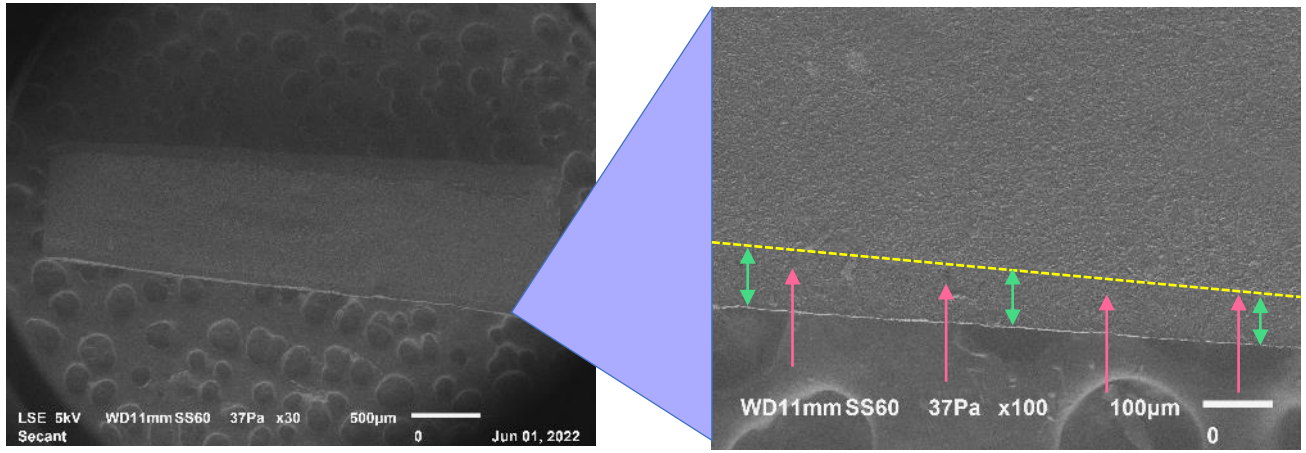
In vivo Studies in Beagle Dogs: Explant Analysis

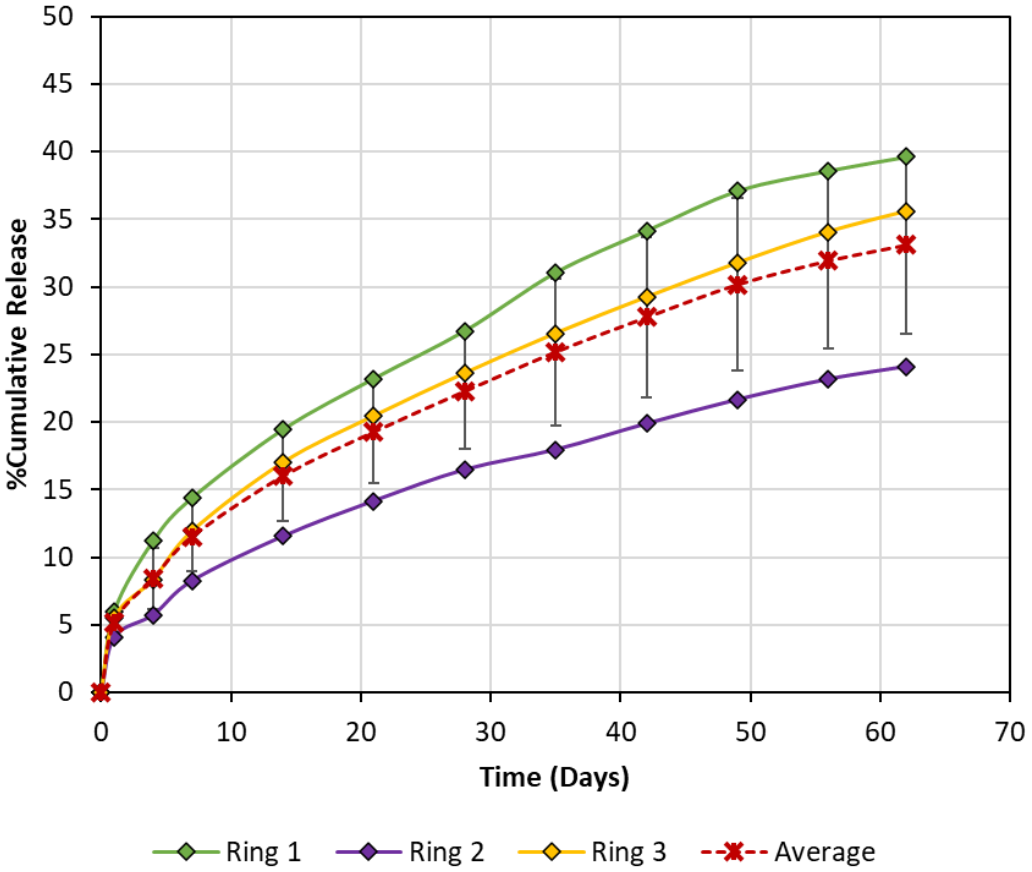
secant group

	Surface	Cross-section
Pre-ingestion		
Post-ingestion		

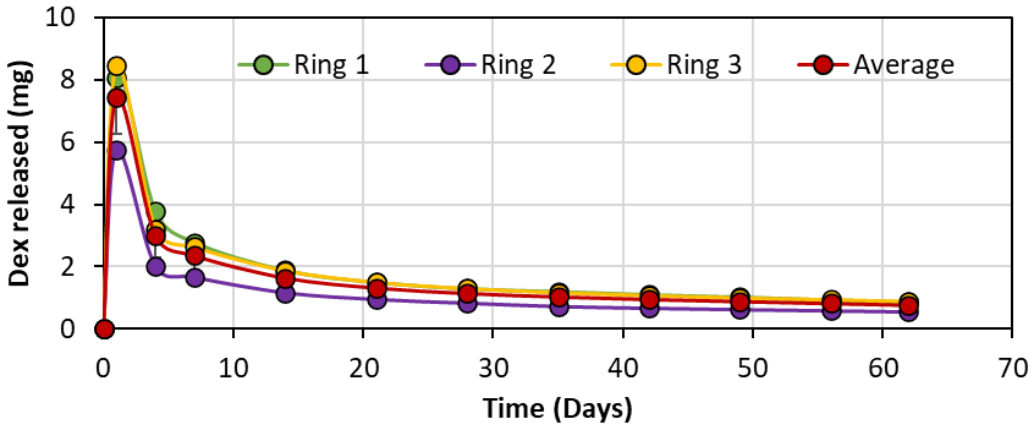
Zone of released Dex

Fluid infiltration

In vitro Release from 30% Dex Loaded PGSU Rings



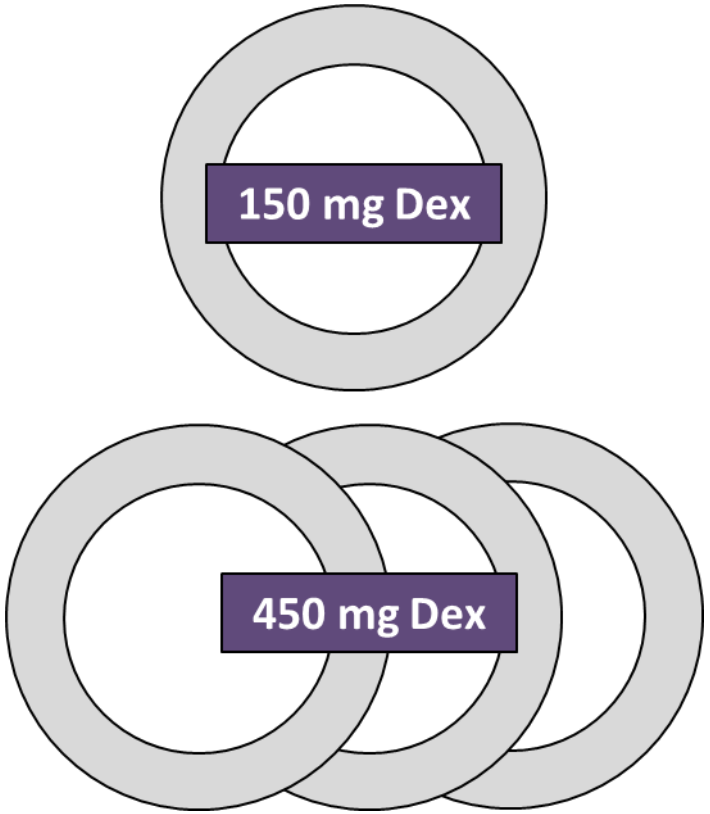
- Distek App 2 was used
- Carried out in SGF (pH 1.2) at 37°C



Ref:
https://www.distekinc.com/products/model-2500-select/

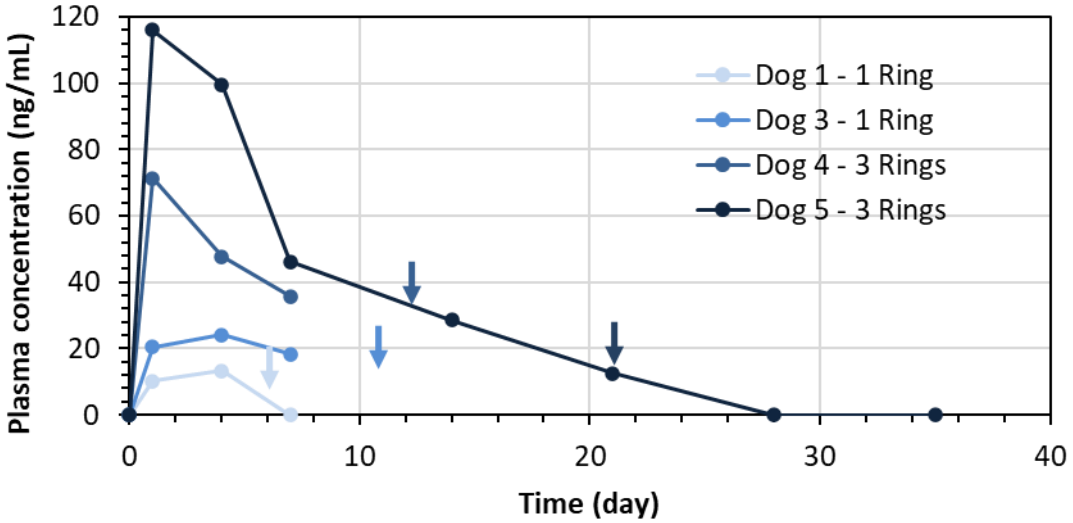
In vivo Studies in Beagle Dogs: Dosage

Each ring weighed 500 mg
150 mg Dexamethasone/Ring

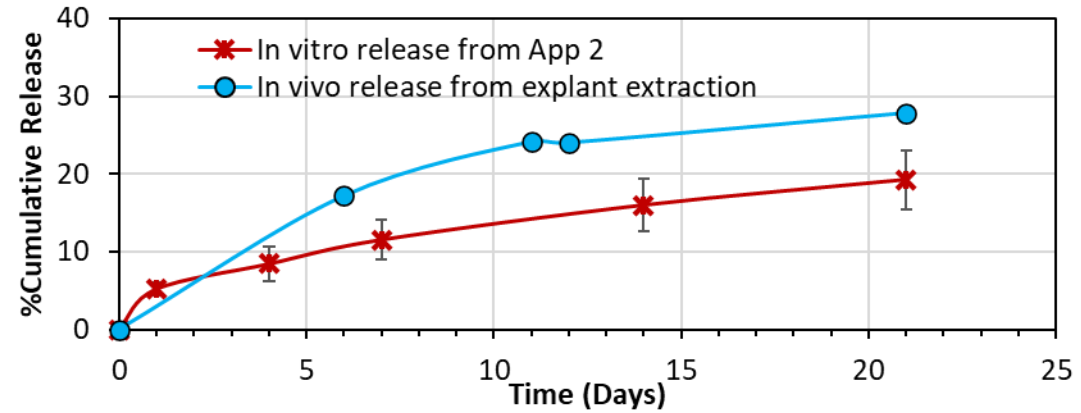


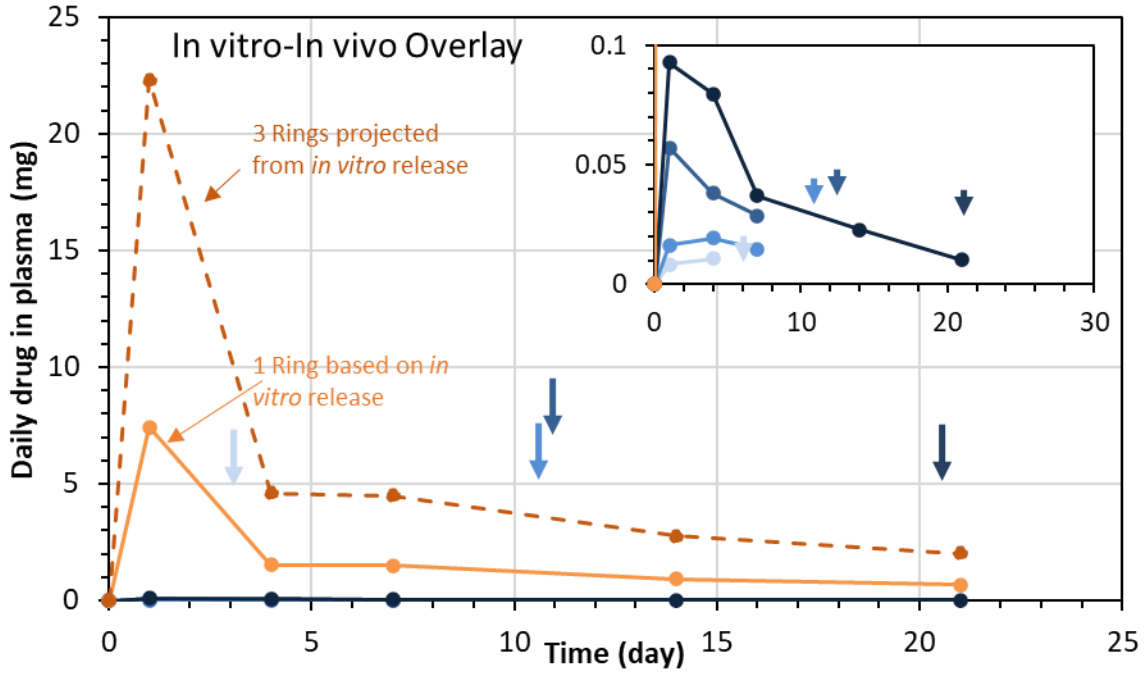
- Dexamethasone is a glucocorticoid used to treat inflammatory conditions in humans as well as dogs.
- Bioavailability of 80%
- Half life 36-54 hours
- Commercial products: Dose in dogs 0.2 – 0.7 mg/kg/day
  - 2-7 mg/day for a 10 kg dog
- Expected daily release based on our *in vitro* data 0.7 - 1 mg/day

In vivo Studies in Beagle Dogs: Comparison with *in vitro* Release



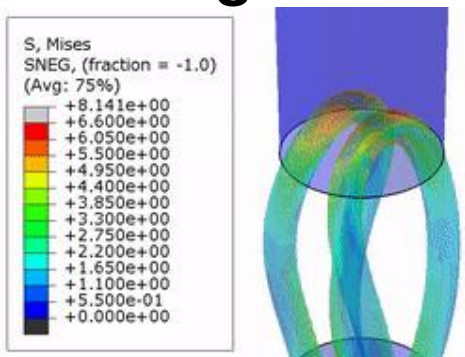
Extraction of Expelled Rings

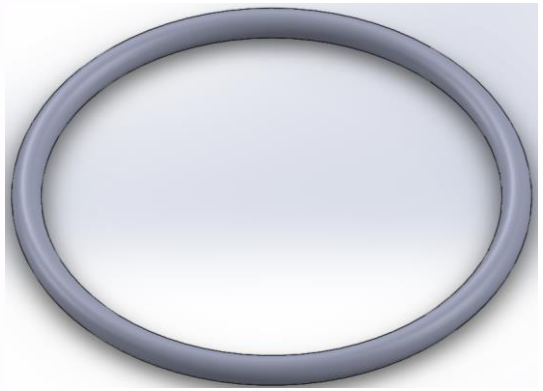




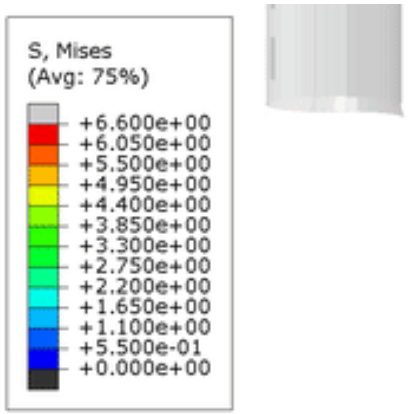
- *In vivo* release is comparable to *in vitro* studies.
- Blood was drawn weekly, which may not capture all the Dex release.
- Dex may be lost to metabolism and clearance.
- Based on explant extraction, 17-28% Dex was released *in vivo.*

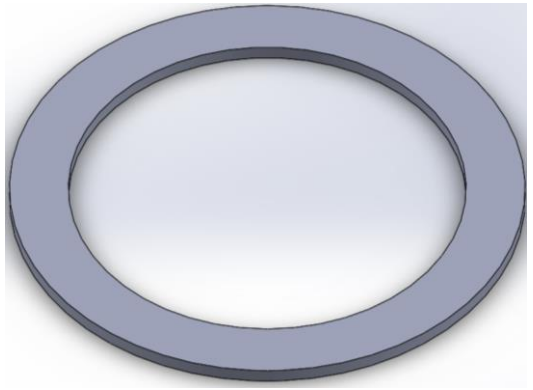
Loading into 000 Capsule



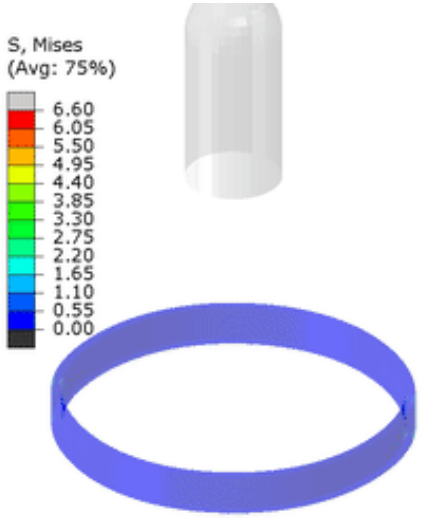


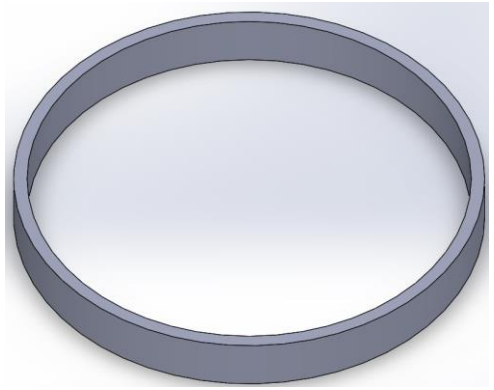
Ring with circular cross section



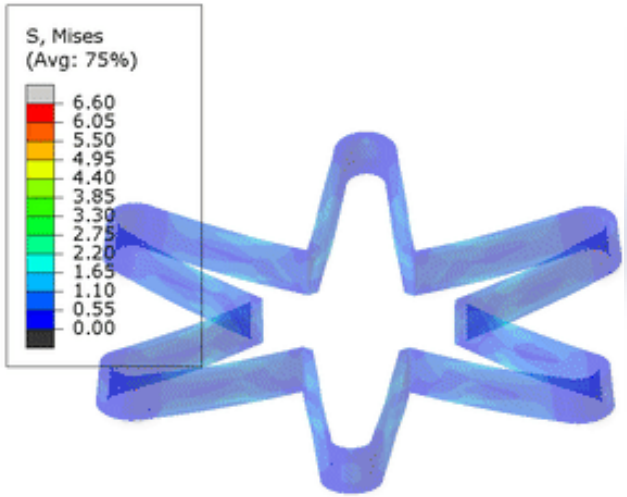


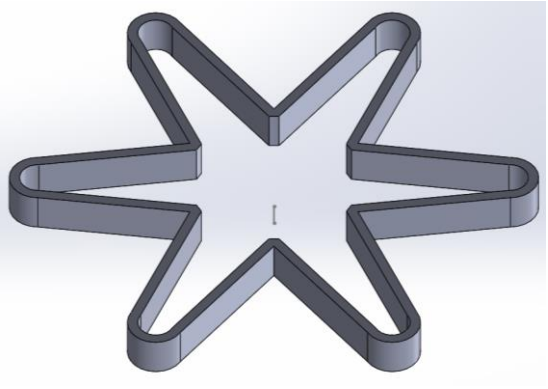
Ring with wide rectangular cross section





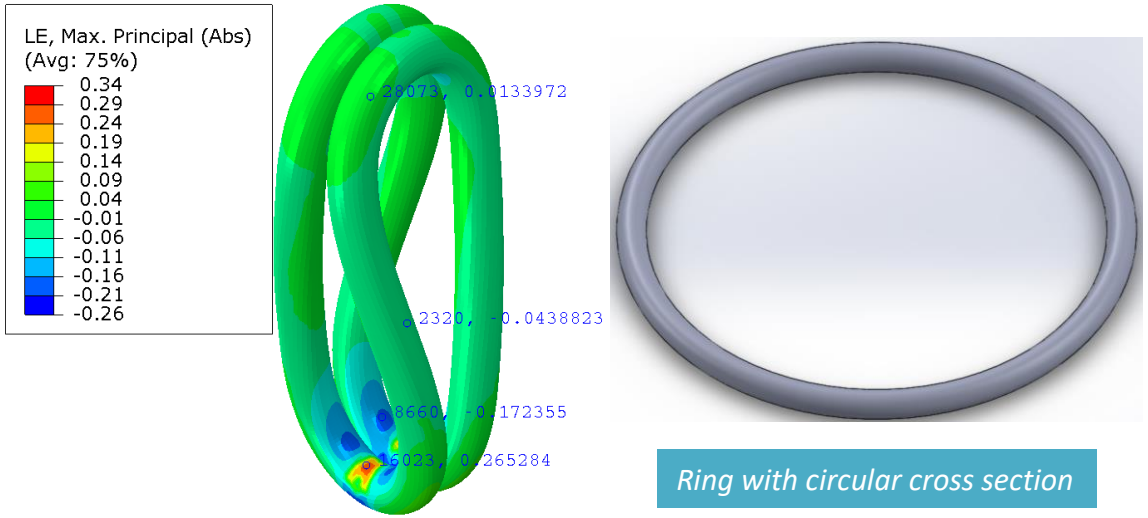
Ring with tall rectangular cross section



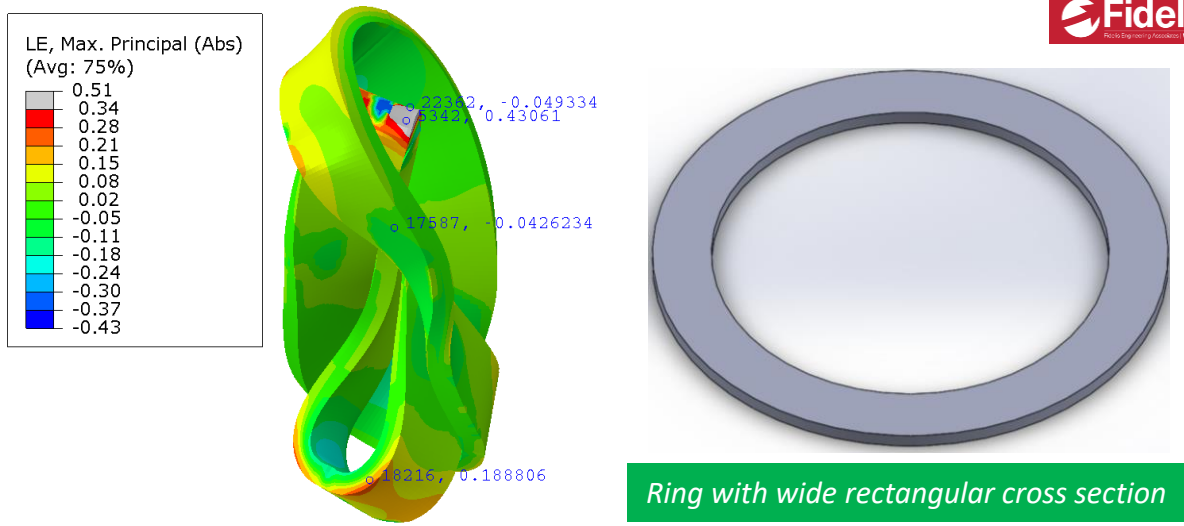


Six-pointed star

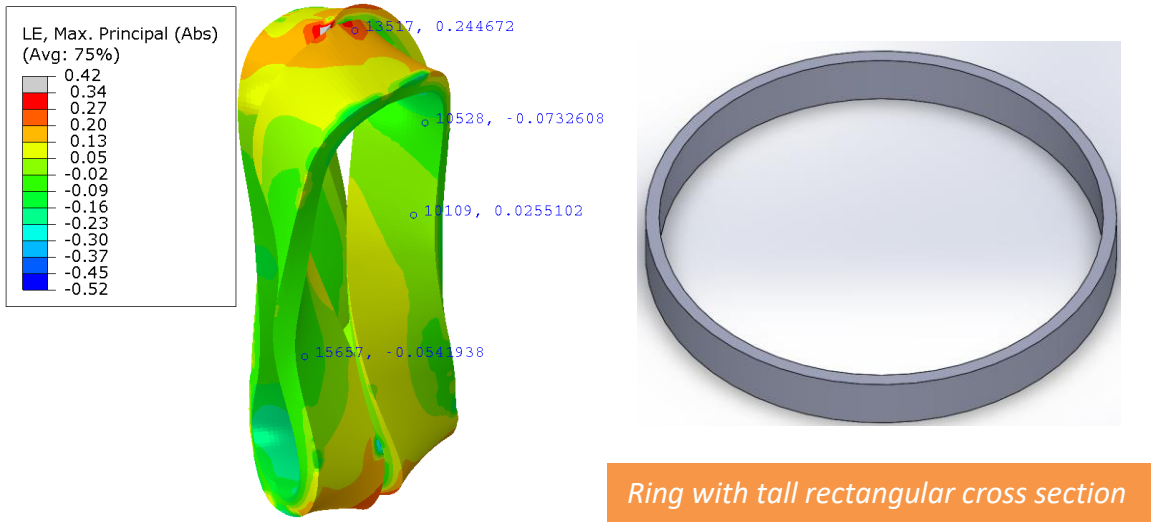
Relaxation in 000 Capsule



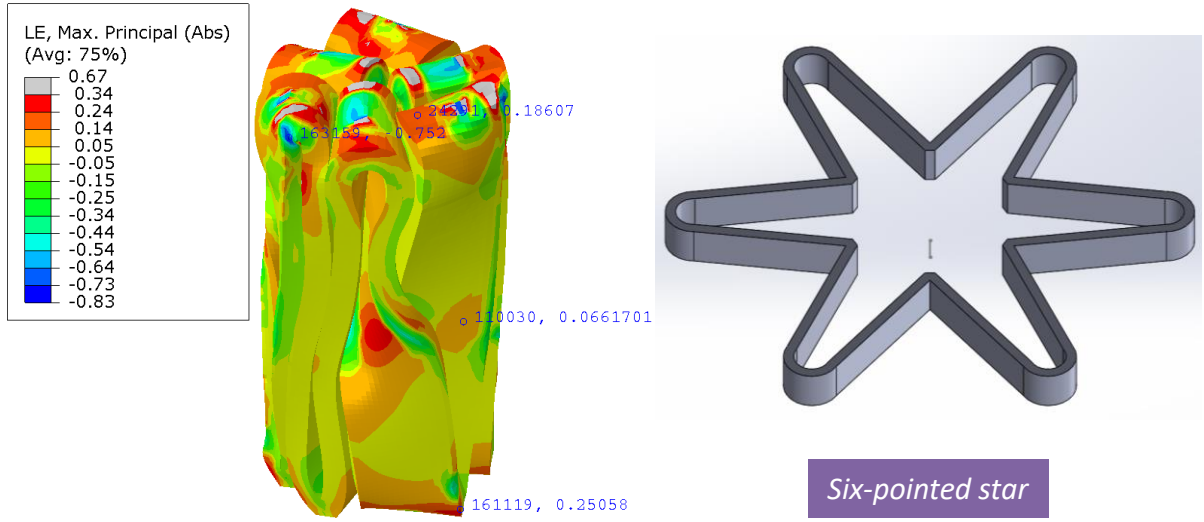
Ring with circular cross section



Ring with wide rectangular cross section

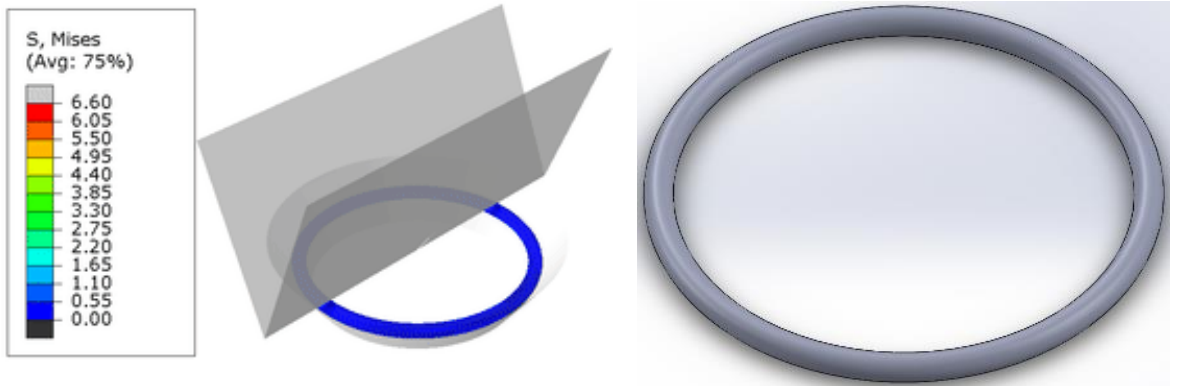


Ring with tall rectangular cross section

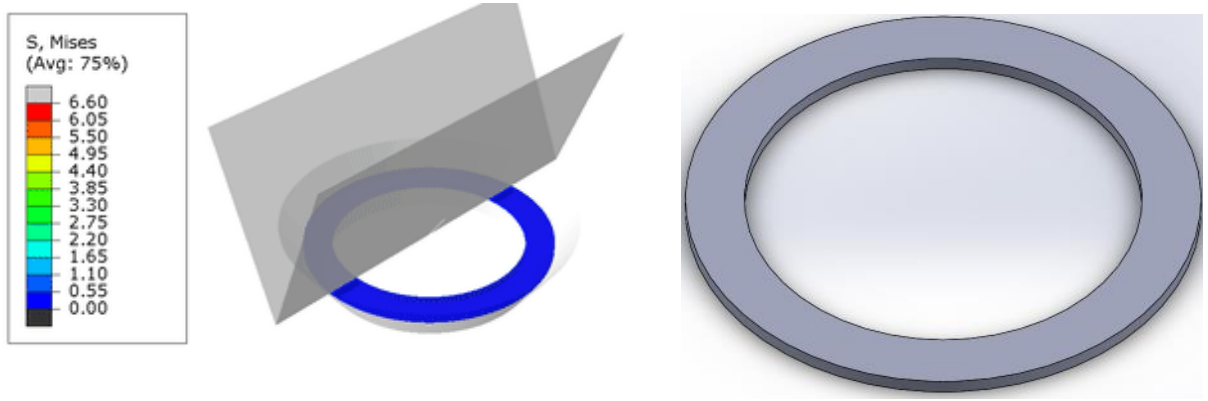


Six-pointed star

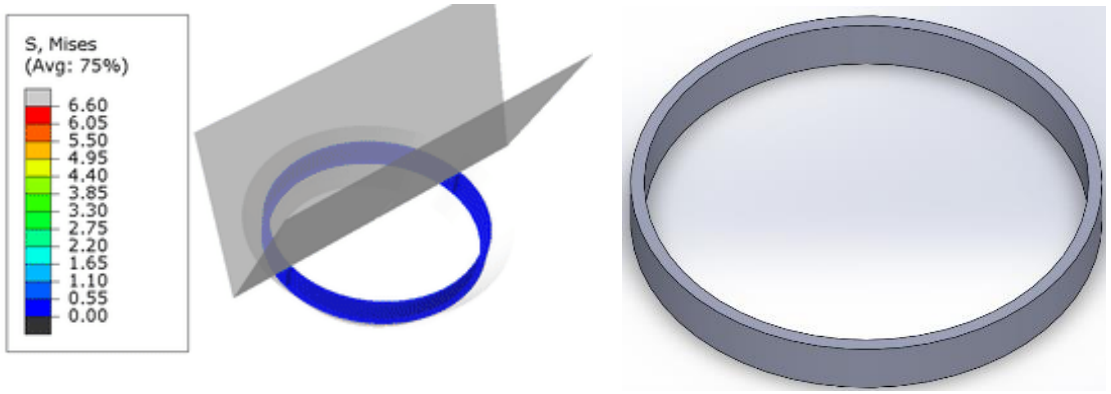
Passage of Deployed Device Through the Gastric Sphincter



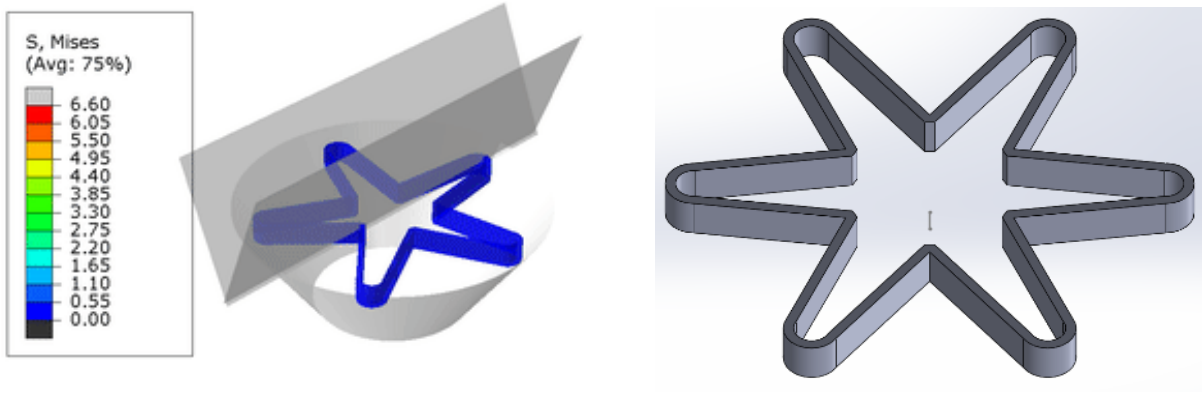
Ring with circular cross section



Ring with wide rectangular cross section



Ring with tall rectangular cross section

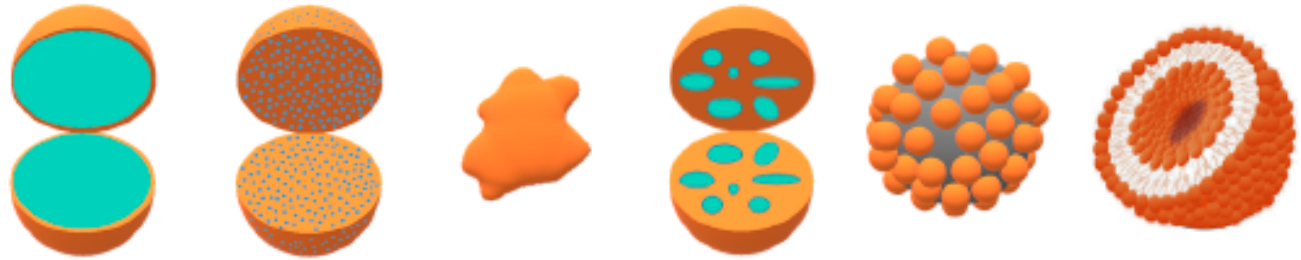


Six-pointed star

Hydralese (PGSU) Microspheres

Microparticulate Drug Delivery System

- Microspheres or microparticles are a multi-particulate drug delivery system.
- They range in size from 1-1000 µm, but particular size ranges are preferred based on route of delivery
  - 10-200 µm for *IM*
  - 5-50 µm for *SC*
  - 1-5 µm for pulmonary inhalation



<u>Advantages of multiparticulate delivery</u>:

- ✓ Delivery route may be parenteral or oral
- ✓ Two or more APIs can be delivered simultaneously while separately formulated
- ✓ Desired rate and duration of API release can be tailored by controlling formulation parameters
- ✓ Targeted drug delivery to desired site can improve patient compliance

Ref:
1. Lengyel, M., Kállai-Szabó, N., Antal, V., Laki, A. J., & Antal, I. (2019). Microparticles, microspheres, and microcapsules for advanced drug delivery. *Scientia Pharmaceutica*, *87*(3), 20.
2. Bale, S., Khurana, A., Reddy, A. S. S., Singh, M., & Godugu, C. (2016). Overview on therapeutic applications of microparticulate drug delivery systems. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, *33*(4).

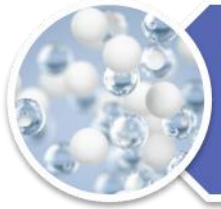
Long-acting Injectable Microparticles on the Market

Commercial Name, Company	API, Indication	Polymer	Method of Manufacturing, Microspheres size	Route of Administration	Duration (weeks)/ Dose (mg)	%Drug Loading (DL)
Lupron Depot®, Takeda	Leuprolide acetate, prostate cancer, endometriosis	PLGA, PLA	Emulsification-solvent evaporation, 11.4±0.5 or 20 µm	IM	4-24 weeks	10.2-20.9
Bydureon®, AstraZeneca	Exenatide, Type II diabetes	PLGA	Emulsification-solvent evaporation, 50 µm	SC	1 week	5.1
Trelstar®, Allergan	Triptorelin pamoate, prostate cancer	PLGA	Spray drying or coacervation, ≤200 µm	IM	4-24 weeks	2.7-11
Signifor® LAR, Novartis	Pasireotide pamoate, acromegaly	PLGA	Emulsification-solvent evaporation	IM	10-60 mg	~34
Sandostatin® LAR, Novartis	Octreotide acetate, acromegaly	PLGA	Emulsification-solvent evaporation	IM	10-30 mg	5.6
Lutrate Depot®, GP Pharm	Leuprolide acetate, prostate cancer	PLA	-	IM	12 weeks	10.67

Ref:
• Zhang, C., Yang, L., Wan, F., Bera, H., Cun, D., Rantanen, J., & Yang, M. (2020). Quality by design thinking in the development of long-acting injectable PLGA/PLA-based microspheres for peptide and protein drug delivery. *International journal of pharmaceutics*, *585*, 119441.

Methods of Manufacturing Hydralese (PGSU) Microparticles

Emulsification-Solvent Evaporation

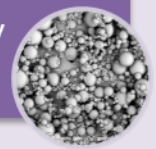


Extrusion-Spheronization

Cryomilling

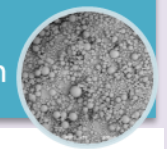
Larger dispersed phase droplets broken down into smaller droplets and stabilized in the continuous phase

Emulsification by Homogenization

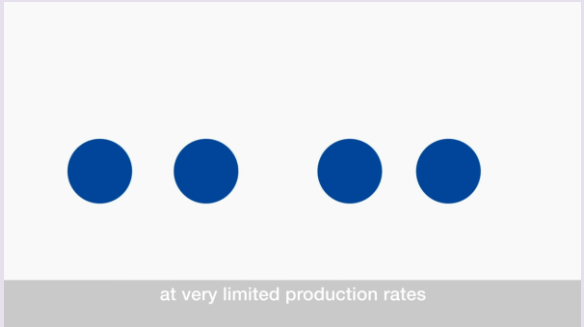


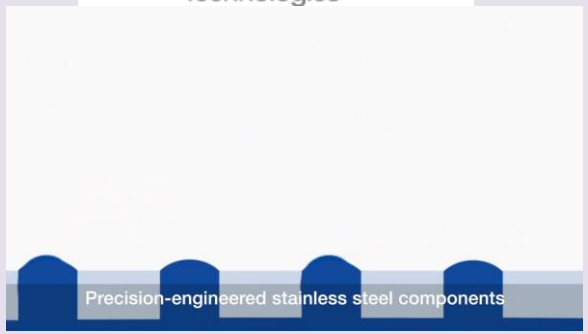
Dispersed phase stabilized in continuous phase by passing through micropores of specific size

Membrane Emulsification



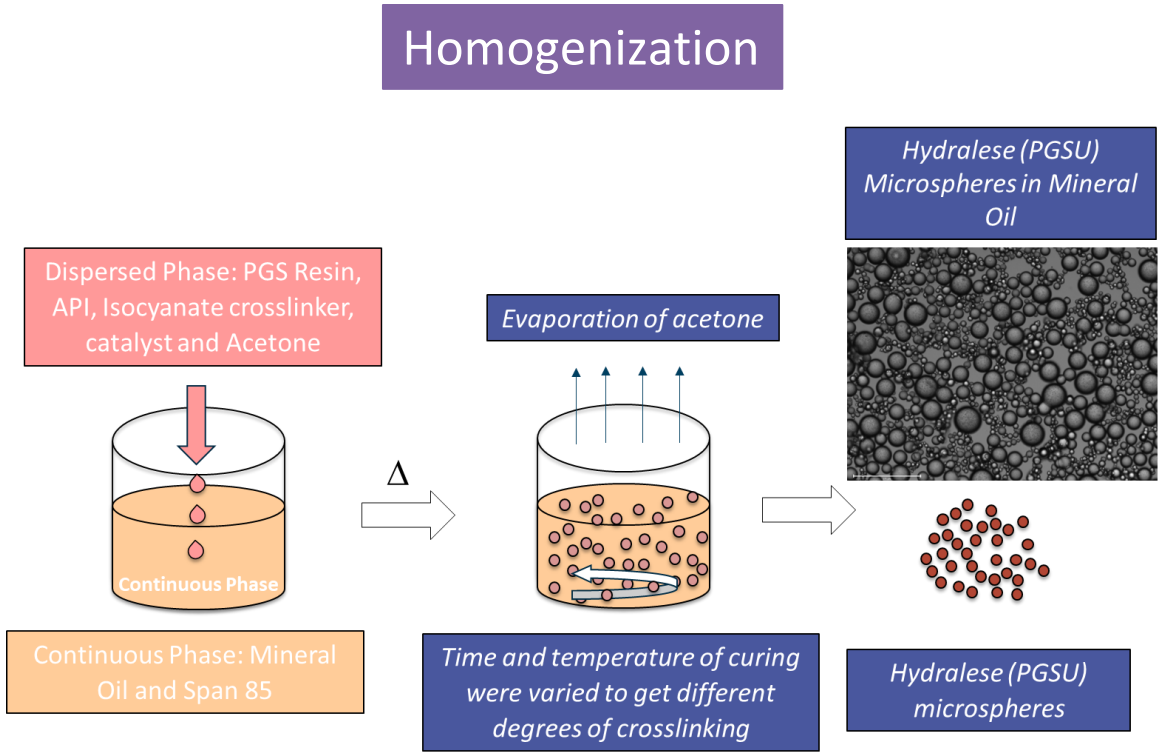
Micropore Technologies



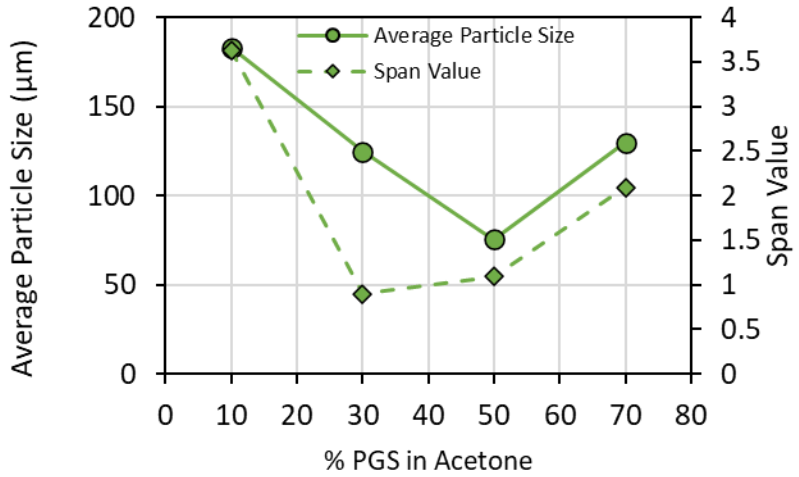


Ref:
https://microporetech.com/

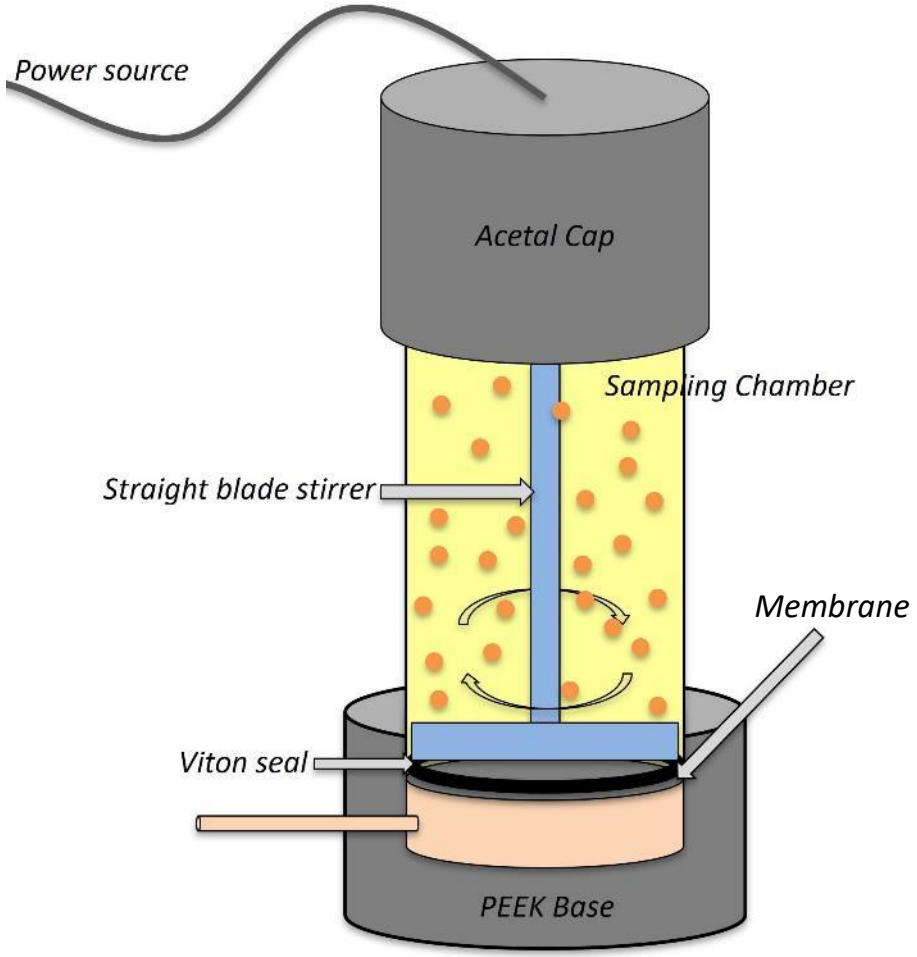
Emulsification-Solvent Evaporation



- Acetone-in-light mineral oil system used
- Crosslinker and catalyst may be present in either the dispersed or continuous phases, or in both.
- %wt PGS in acetone may be between 10-70%
- API may be dissolved or dispersed in acetone.
- Larger average particle sizes are obtained with suspended API in DP.



Emulsification-Solvent Evaporation



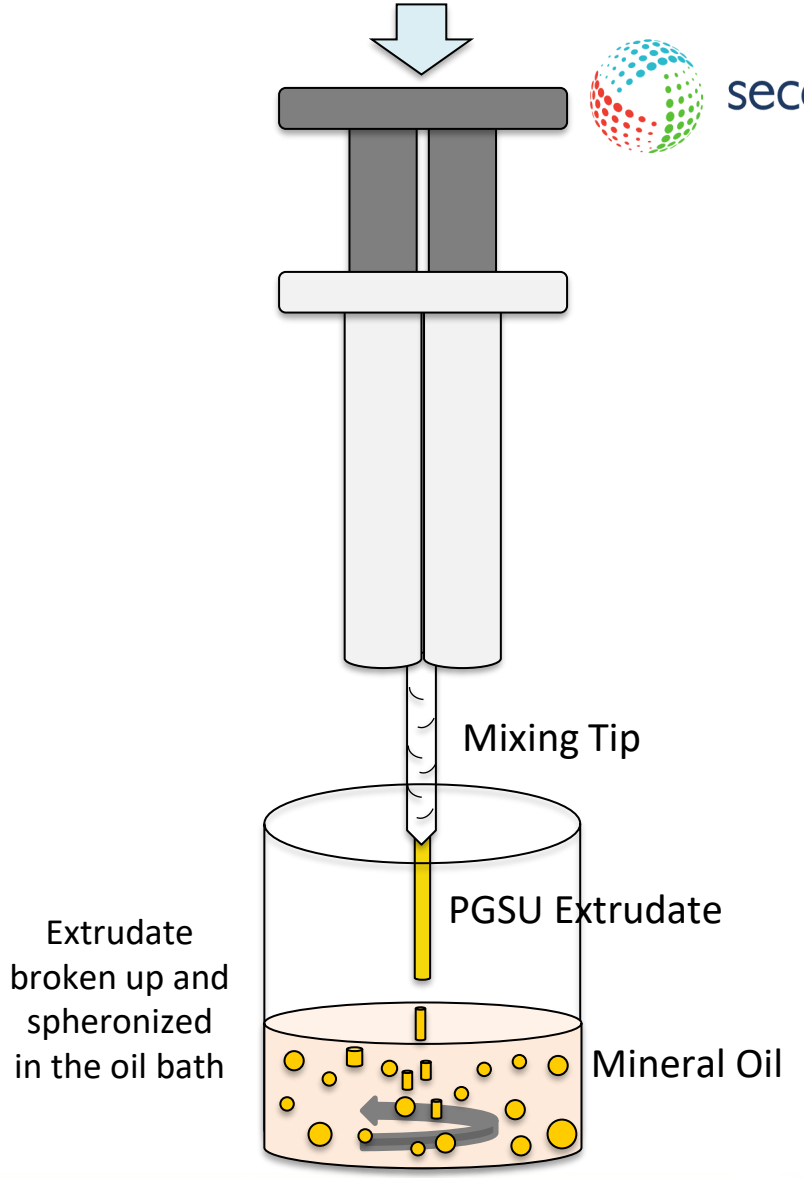
Membrane Emulsification

- Acetone-in-light mineral oil system used
- Crosslinker and catalyst may be present in the dispersed or continuous phases, or both.
- %wt PGS in acetone maybe between 10-70%
- LDC-1 from Micropore Technologies is a lab scale setup.
- Only applicable to API soluble in acetone

Extrusion-Spheronization

- Solvent-free process
- Dual barrel syringe is used to introduce the extrudate into an oil bath
- Ideal for APIs that are insoluble in acetone
  - No physical modification of API
  - Low possibility of the API reacting with the crosslinker
- Results in smaller particle sizes obtained for microspheres

Batch #	Average Particle Size (µm)	Span Value
1	81.2	2.97
2	79.3	2
3	50.3	1.7

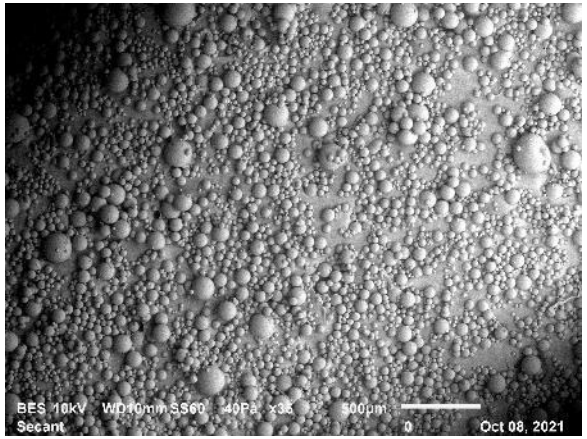


Size Distribution of PGSU Microspheres

secant group

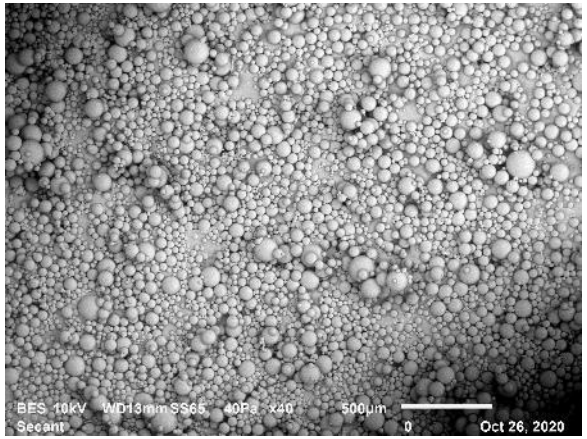
Homogenization

800 rpm

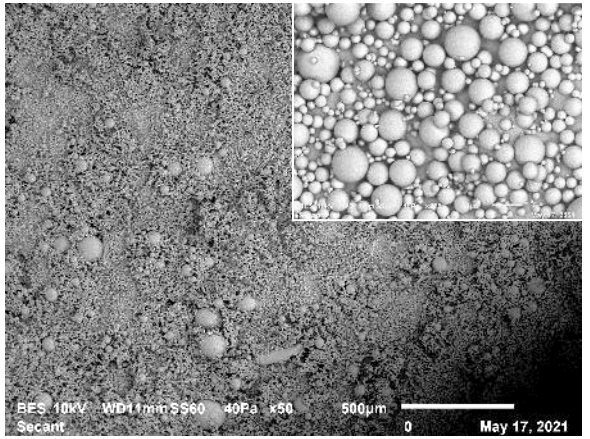


Membrane Emulsification

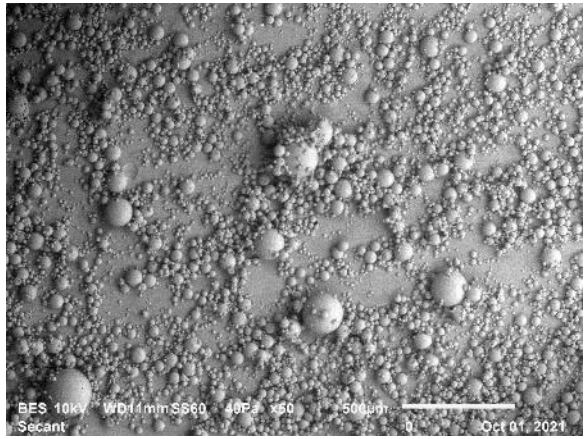
10 µ membrane



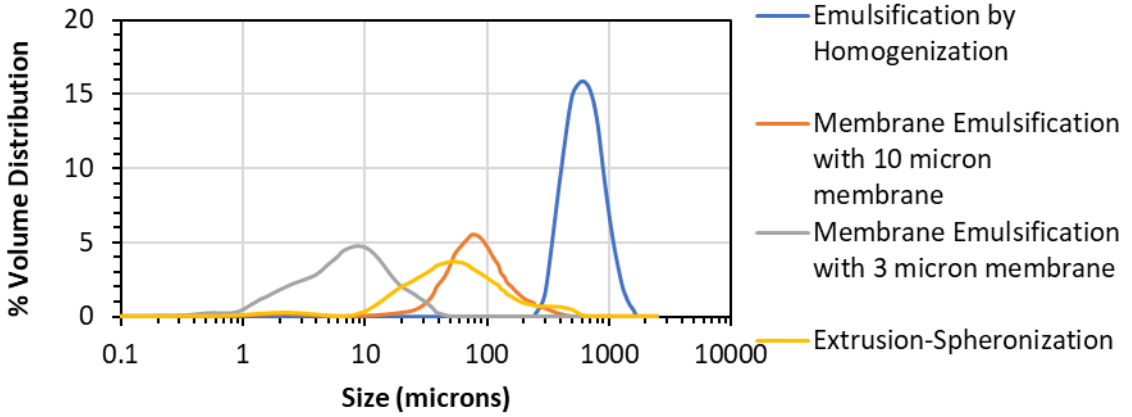
3 µ membrane



Extrusion-Spheronization



Lower average particle size and narrower size distribution achieved by membrane emulsification



Scaling-up Manufacture of Microspheres

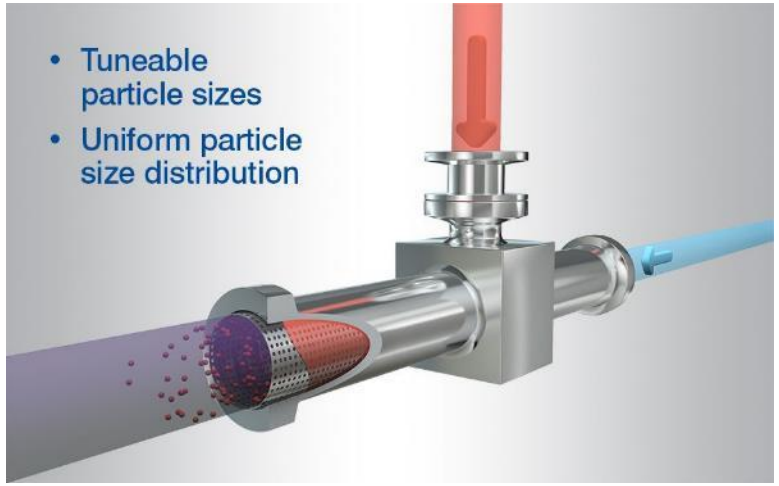
secant group

Homogenization

700 g continuous phase

Membrane Emulsification

Micropore Technologies



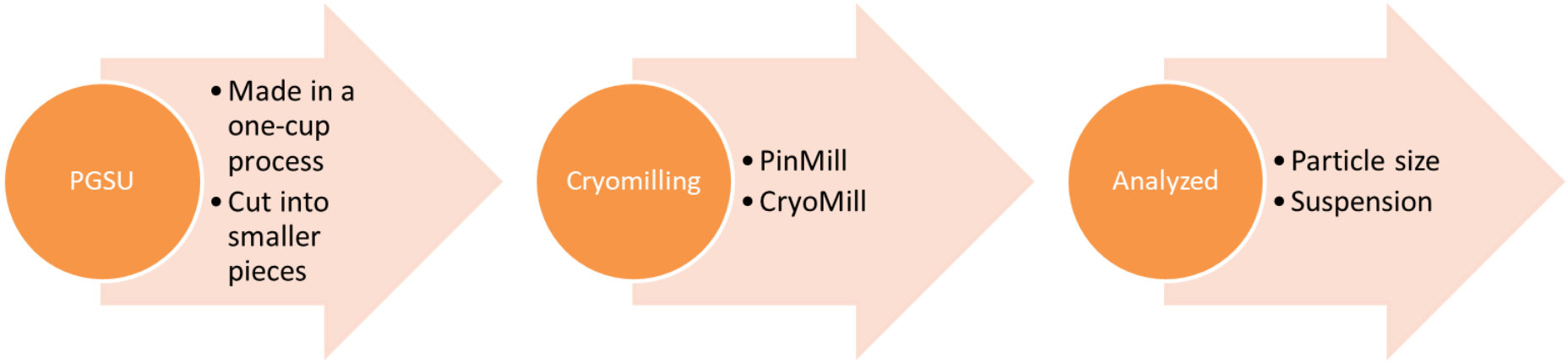
Extrusion-Spheronization

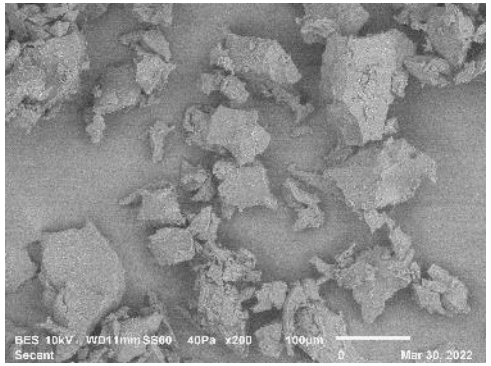
300 g continuous phase

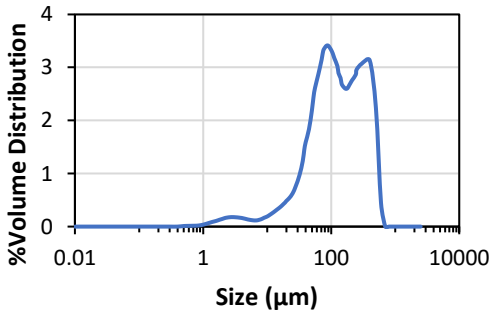
- Homogenization and extrusion carried out under N_2
- Addition of dispersed phase or extrudate at a controlled rate
- High stirring speed (up to 1500 rpm) may be applied.
- Multiple propeller blades may be attached to the propeller shaft.

Ref:
- https://www.micropore.co.uk/

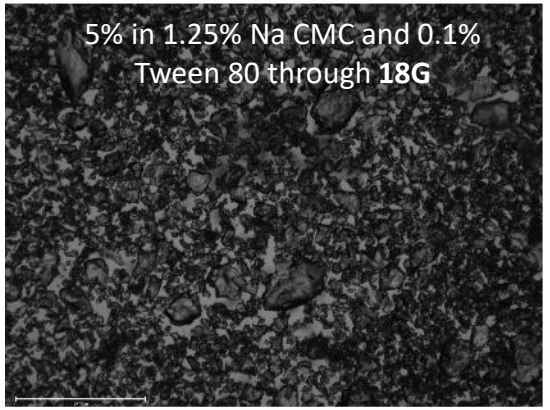
PGSU Microparticles by Cryomilling







- Kinetic sand-like irregularly shaped particles
- 5% cryomilled PGSU dispersed in 1.25% Na CMC and 0.1% Tween 80 solution
- Passes 18G – 838 µm needles

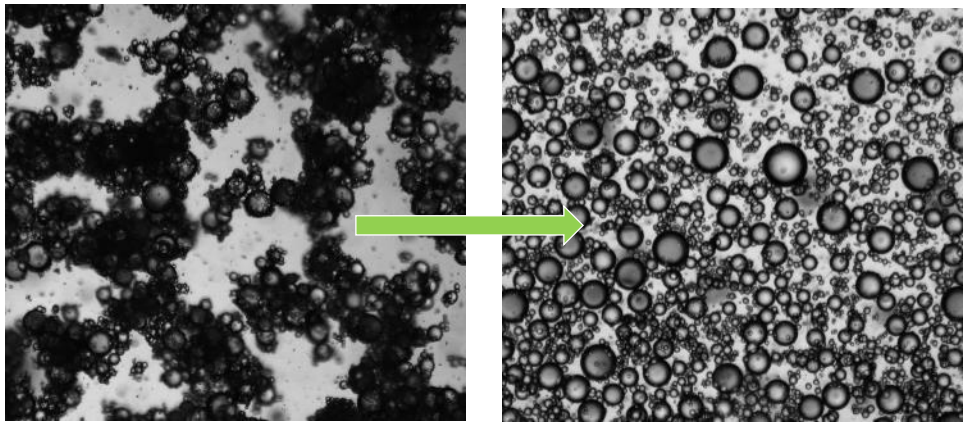


Average size = 174.6 µm

Suspension and Injectability of PGSU Microspheres

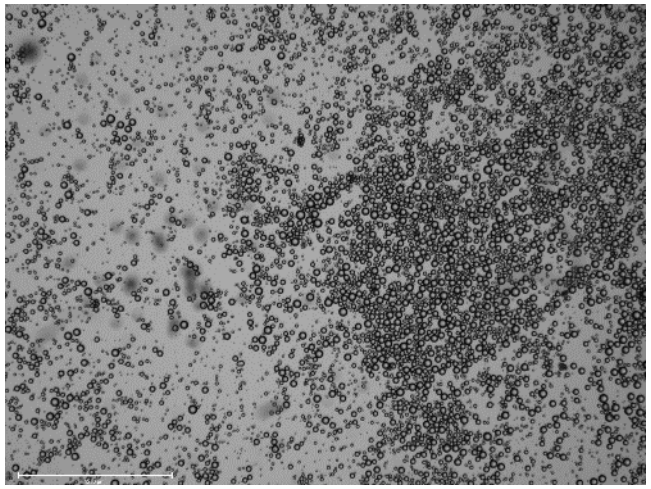
In Na CMC *Addition of Tween 80*

30% PGSU Microspheres suspension in water + 1.25% Na CMC + 0.1% Tween 80



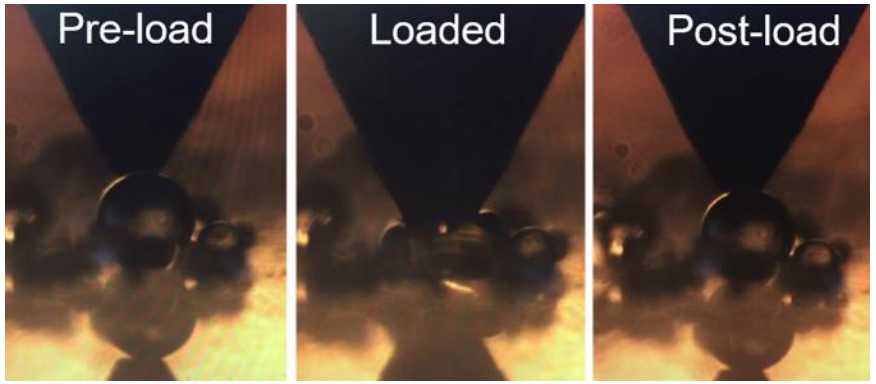
- Microspheres must have a uniform particle size/narrow dispersity to successfully suspend.
- Sodium carboxymethyl cellulose and Tween 80 are commonly used in marketed parenteral formulation up to 1.35% and 0.2%, respectively.
- Sodium carboxymethyl cellulose (Na CMC, 95 kg/mol) acts as a viscosity builder.
- Tween 80 is a surfactant that helps break apart the aggregates.

0.5% PGSU Microspheres through 30G

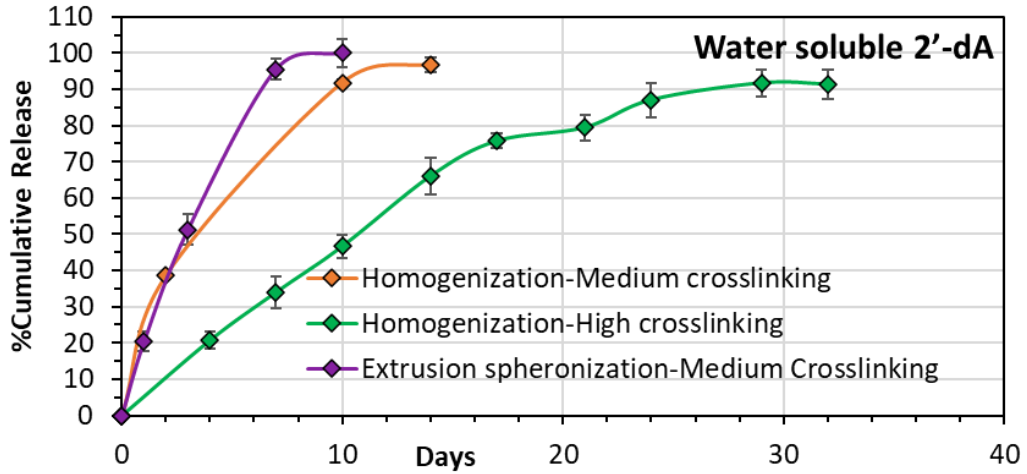


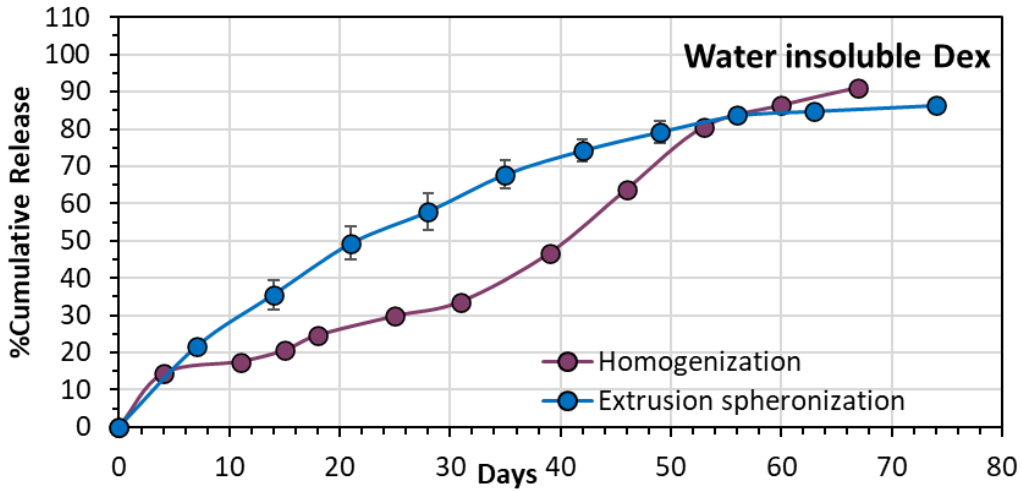
Microsphere Size Range	Passed Through
< 43 µm	30G and 27G
43-75 µm	30G and 27G
75-106 µm	27G, 23G and 22G
106-212 µm	23G and 22G
212-300 µm	22G
>300 µm	None

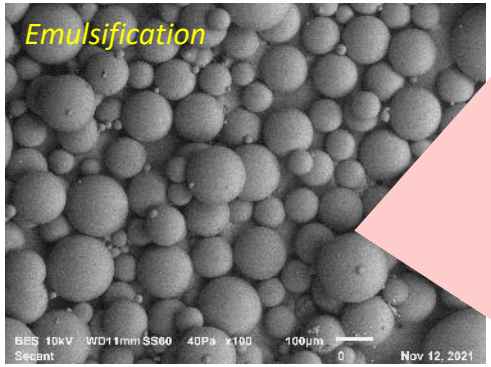
Micro-indentation of PGSU Microspheres

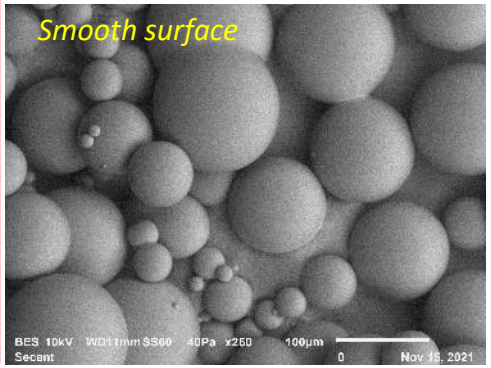


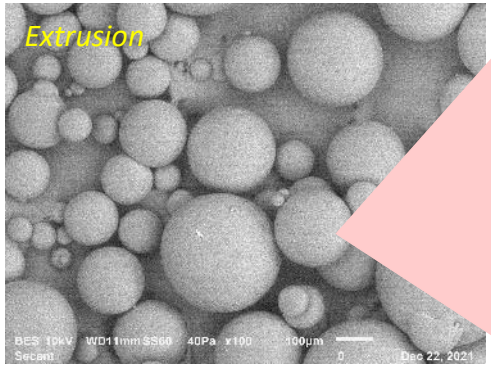
In vitro Release from PGSU Microspheres

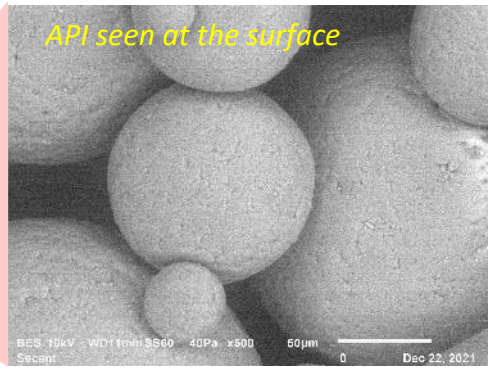




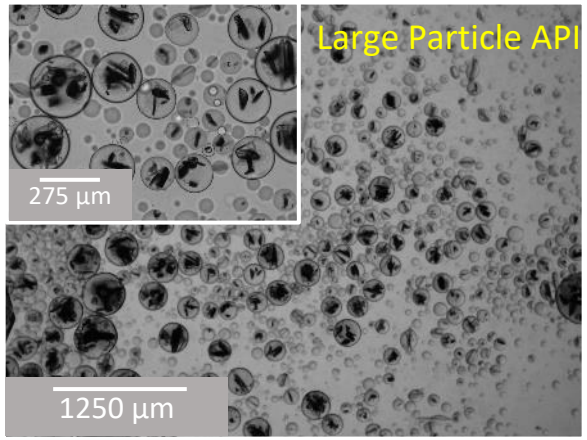


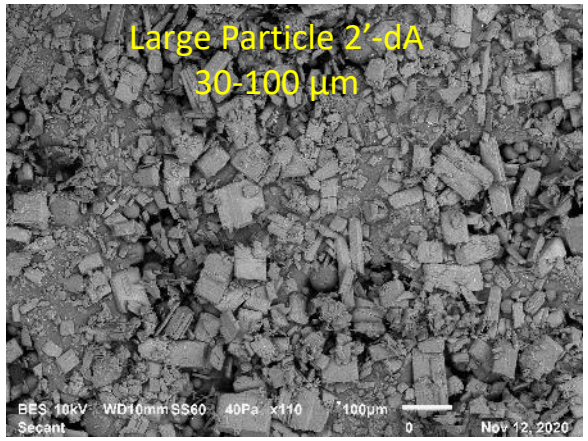


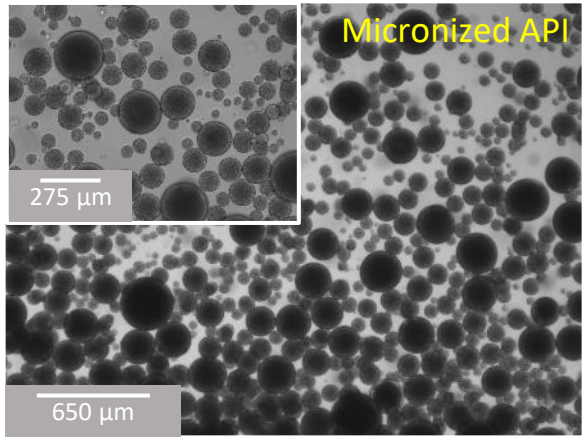


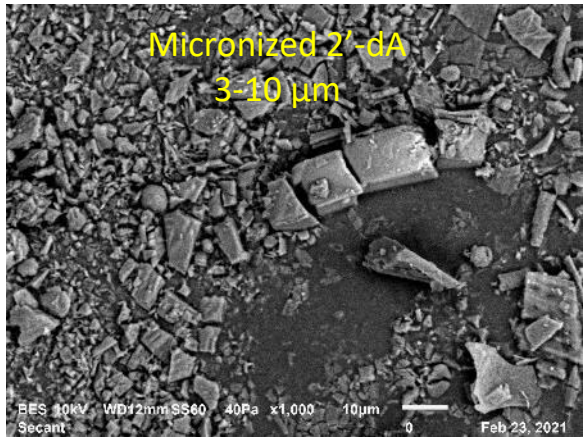


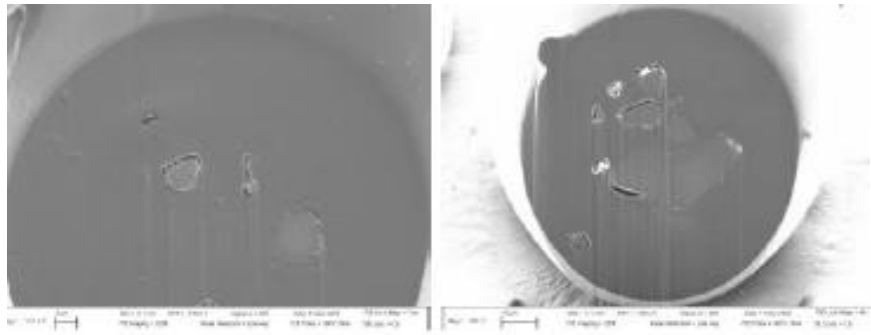
Effect of API Size on PGSU Microspheres

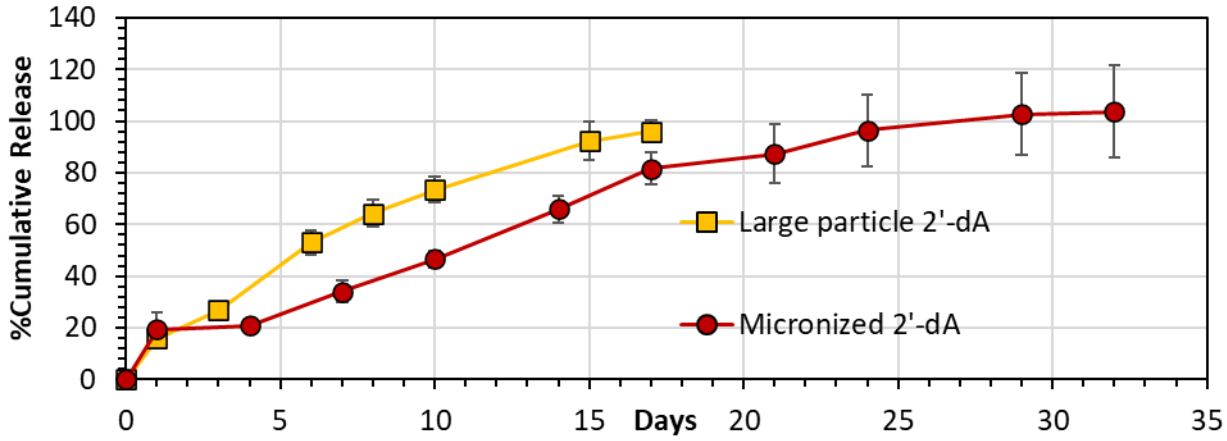






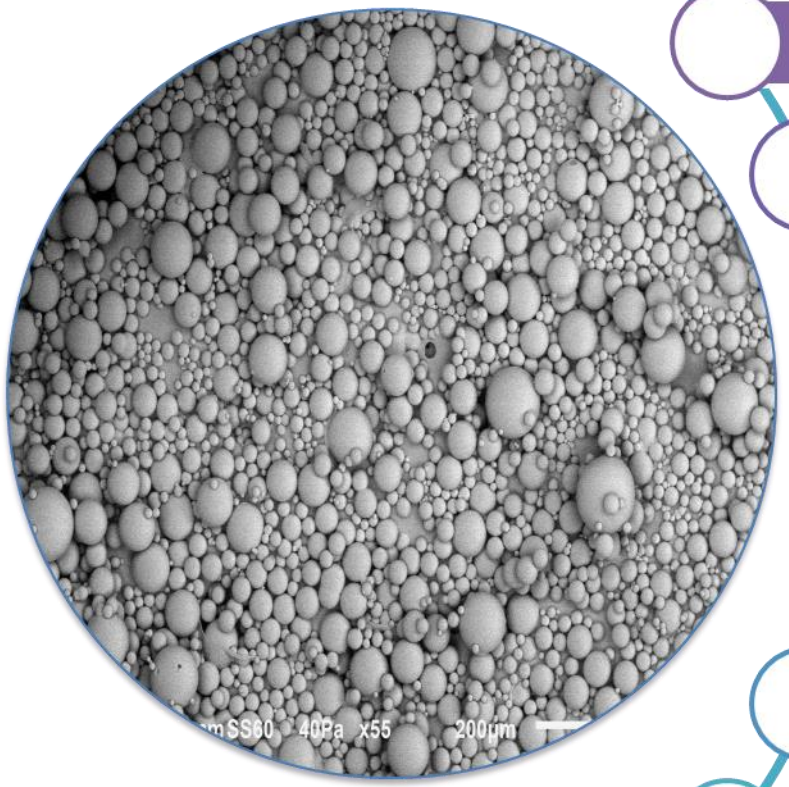






Micronized 2'-dA is preferrable as it is better loaded in the microspheres

Factors Affecting Release of API from PGSU Microspheres



- Particle size/surface area of the microspheres
- % drug loading in PGSU microspheres
- Solubility of API in water
- Physical form of the API: crystalline vs amorphous
- Crosslinking density of PGSU
- Particle size of the API if present in crystalline form
- Process of manufacture

The Value of Partnership with Secant Group

secant group

End-to-end Drug Delivery Solution

Secant as CRO/CDO SanaVita as CMO

Secant as Materials Supplier

Unlock Unrealized Potential

PGSU can positively impact:
- Patient compliance
- Global health
- IP lifecycle management
- New patient populations
- Expanded formulations
- Broader API candidates

APIs, Generics, Biologics, Biosimilars, Vaccines

Compatible APIs
- Small molecule
- Peptides
- Proteins
- Antibodies

+

Hydralese (PGSU) Novel Delivery Technology

New Delivery Forms
- Implants
- Micro devices
- Microspheres
- Gastroretentive devices
- Textile coatings

Acknowledgements

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- ❑ Mohamed Elkhodiry, Ph.D. (Engineer II)
- ❑ Sumit Kumar (Director, Strategic Partnerships and Pipeline Development)

Thank you for your attention!

Questions?