Implantable Systems and Microparticle Depots

Meeting the Formulation and Manufacturing Challenges of Long-Acting Drug Delivery

HEALTH

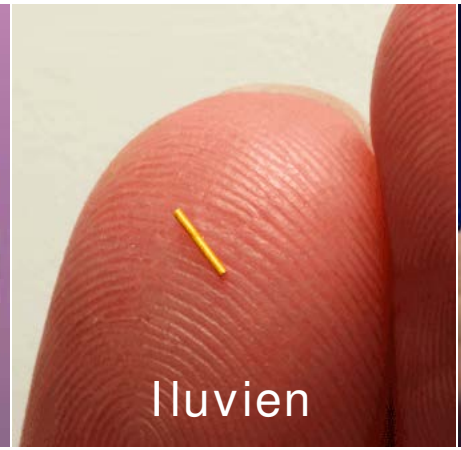
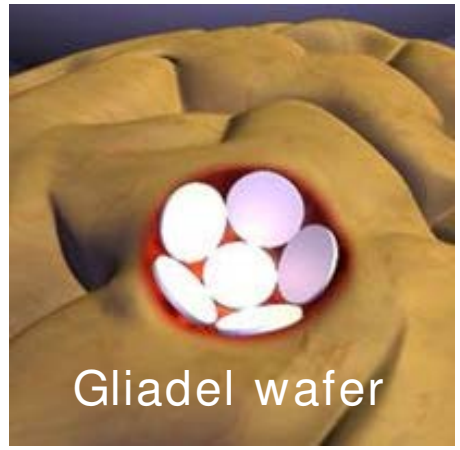
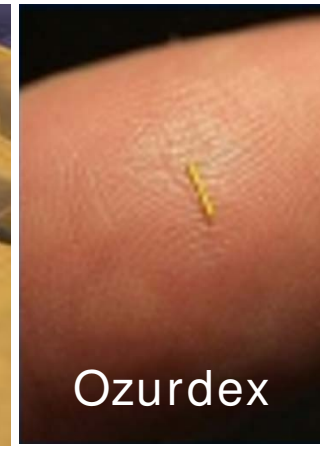
Introduction

- What are implants and depots?
- Why implants and depots?
  - Improved patient compliance & improved efficacy = Improved outcomes
    - Reduced administration frequency
    - Bypasses gastric and hepatic first pass degradation of API
    - Controlled drug delivery level
    - Long-lasting drug delivery
    - Local or systemic drug delivery
  - Revenue potential of novel dosage form
  - Drug lifecycle management
  - IP

Examples Of Implants

Biodurable

Bioresorbable

Intravaginal	Intraocular		Sub-cutaneous	Intrathecal	Intraocular
 Nuvaring Estring	 Occusert	 Iluvien	 Implanon (Nexplanon) Norplant (Jadelle)	 Gliadel wafer	 Ozurdex
Contraception HRT Cancer Moisturizing ~ weeks 1 year (2020)	Uveitis Diabetic Macular Edema ~ years		Contraception Diabetes Opioid Addiction ~ years	Recurrent Glioma ~ weeks	Glaucoma AMD ~ months

Examples Of Depots

		Dosing Frequency
Vivitrol (naltrexone for extended-release injectable suspension)	**Vivitrol® by Alkermes** – Active Ingredient: Naltrexone – Route of Administration: Intramuscular – Approval Date: 1984 – Indicated for the treatment of alcohol/opioid dependence	**Every 4 weeks**
Sandostatin® LAR Depot (octreotide acetate for injectable suspension) 10mg • 20mg • 30mg	**Sandostatin® LAR Depot by Novartis** – Active Ingredient: Octreotide – Route of Administration: Subcutaneous – Approval Date: 1998 – Indicated for treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors and VIP-secreting tumors	**Every 4 weeks**
Arestin® minocycline HCl 1mg MICROSPHERES	**Arestin® by OraPharma** – Active Ingredient: Minocycline HCl – Route of Administration: Periodontal – Approval Date: 2001 – Indicated as an adjunct to scaling and root planning (SRP) procedures for reduction of pocket depth in patients with adult periodontitis	**Variable**
RisperdalCONSTA risperidone Long-Acting Injection 12.5mg, 25mg, 37.5mg, 50mg	**Risperdal Consta® by Janssen** – Active Ingredient: Risperidone – Route of Administration: Intramuscular – Approval Date: 2003 – Indicated for the treatment of schizophrenia and bipolar I disorder	**Every 2 weeks**
LuproDepot® (leuprolide acetate for depot suspension)	**Lupron Depot® by AbbVie** – Active Ingredient: Leuprolide acetate – Route of Administration: Intramuscular – Approval Date: 1989 – Multiple indications including prostate cancer, central precocious puberty, fibroids and endometriosis	**Every 1, 3 or 6 months**

Part 1

Biodurable and Bioresorbable Implants

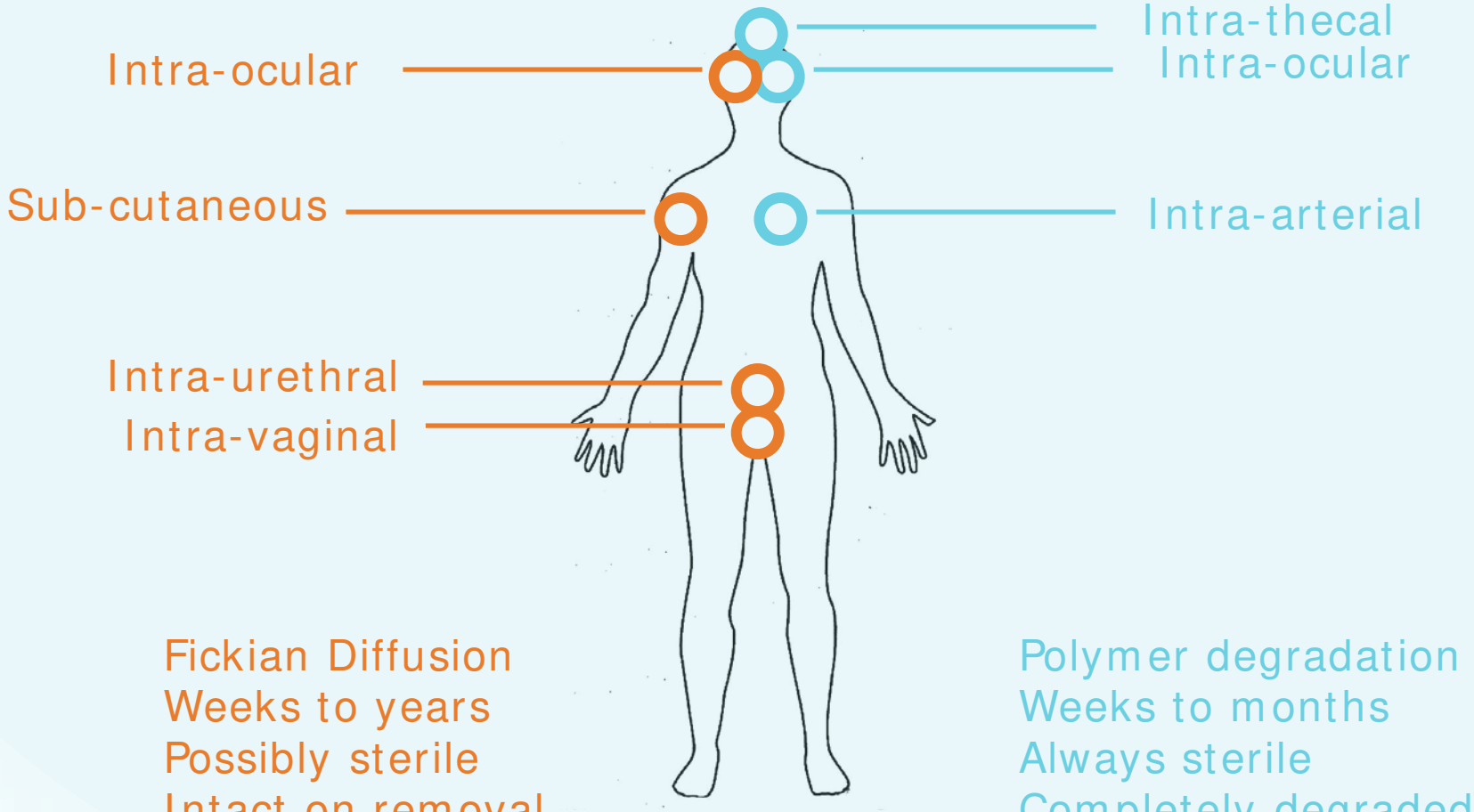
HEALTH

Short to long term drug delivery
explantation straightforward

Short to medium term drug delivery
explantation undesired or impossible)

BIODURABLE IMPLANTS

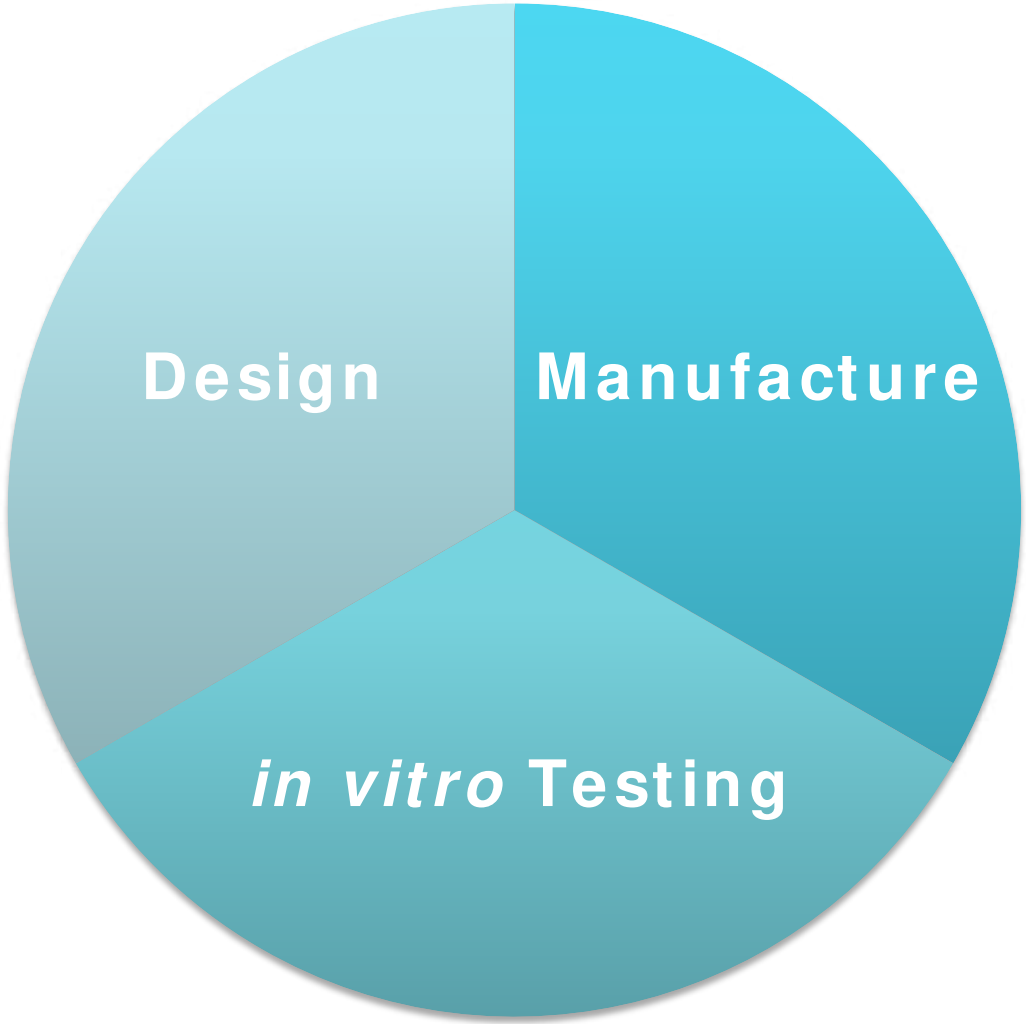
BIO-RESORBABLE IMPLANTS



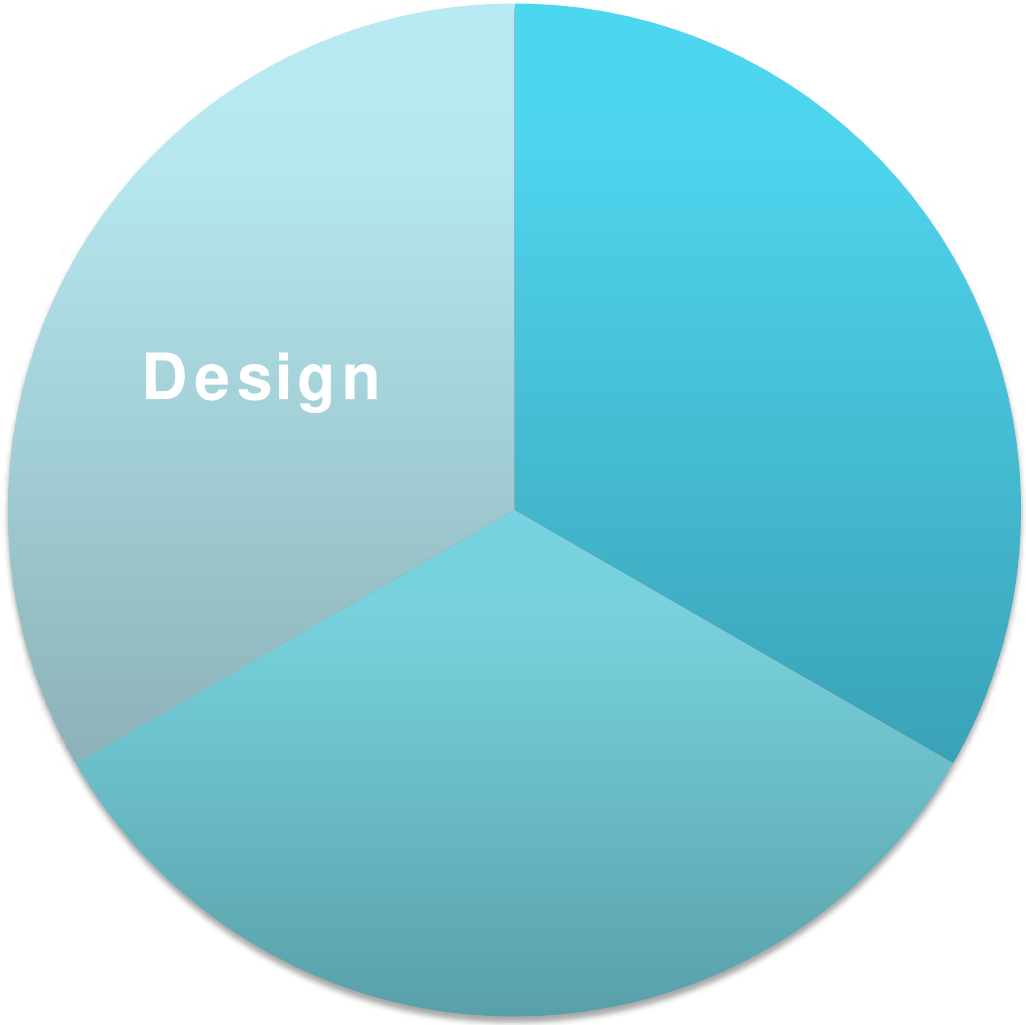
Fickian Diffusion
Weeks to years
Possibly sterile
Intact on removal

Polymer degradation
Weeks to months
Always sterile
Completely degraded

The Key Challenges

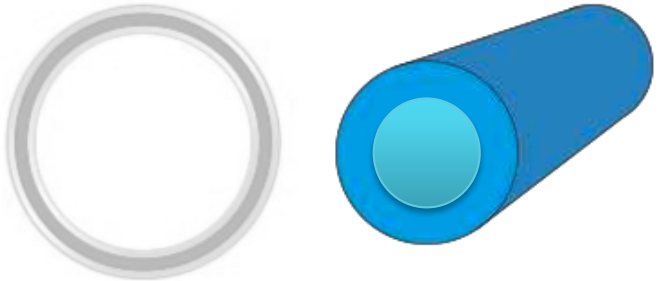


The Key Challenges

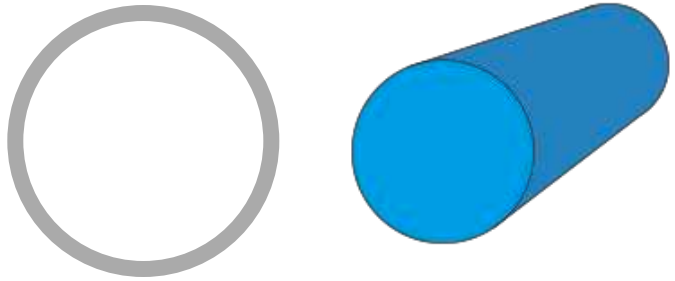


Matrix or Reservoir?

Core-sheath Reservoir Implant

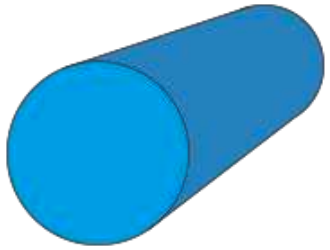


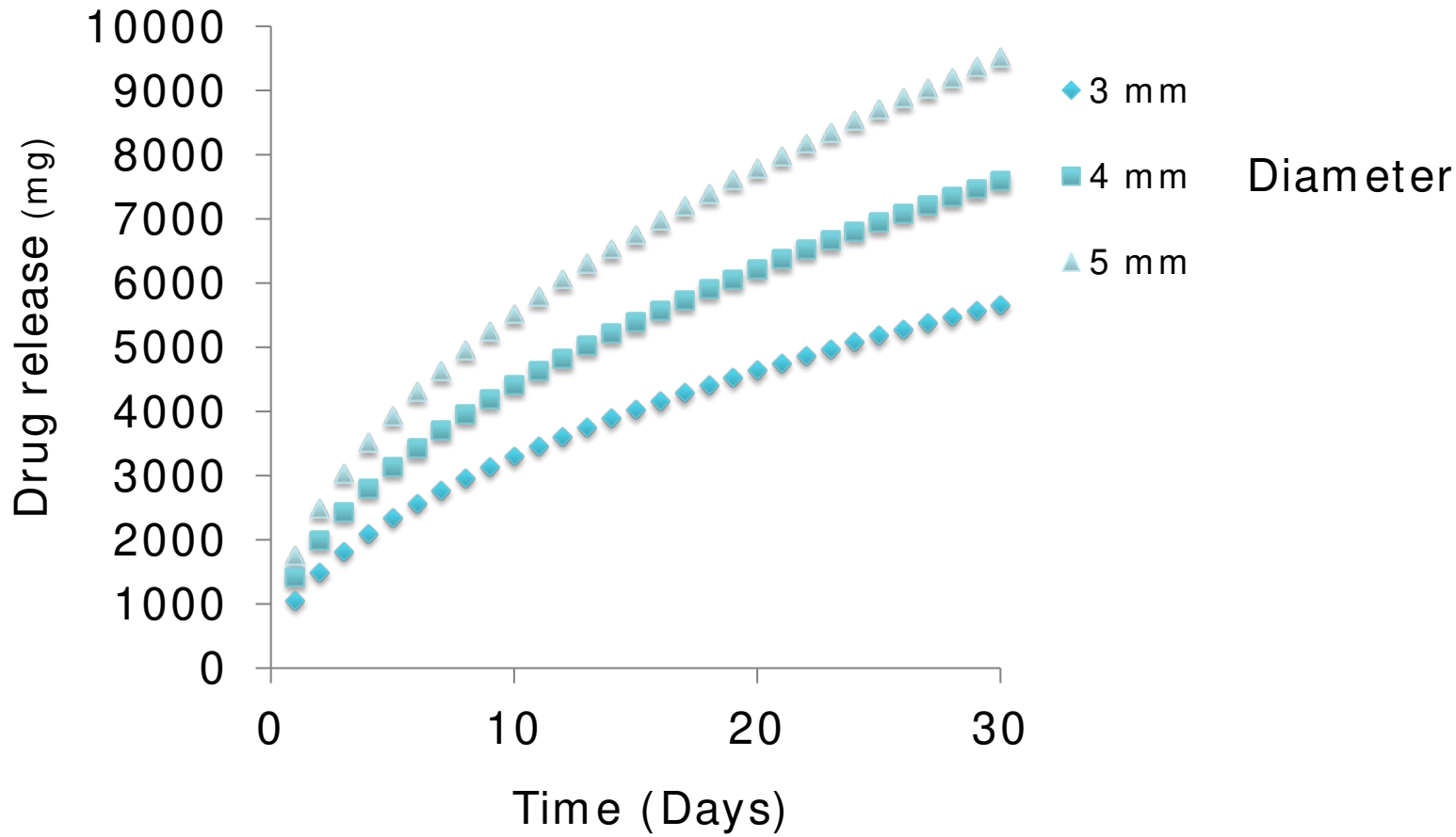
Matrix Implant



What Dimensions?

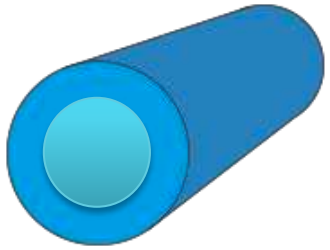
Rod Diameter Affects Drug Release Rate

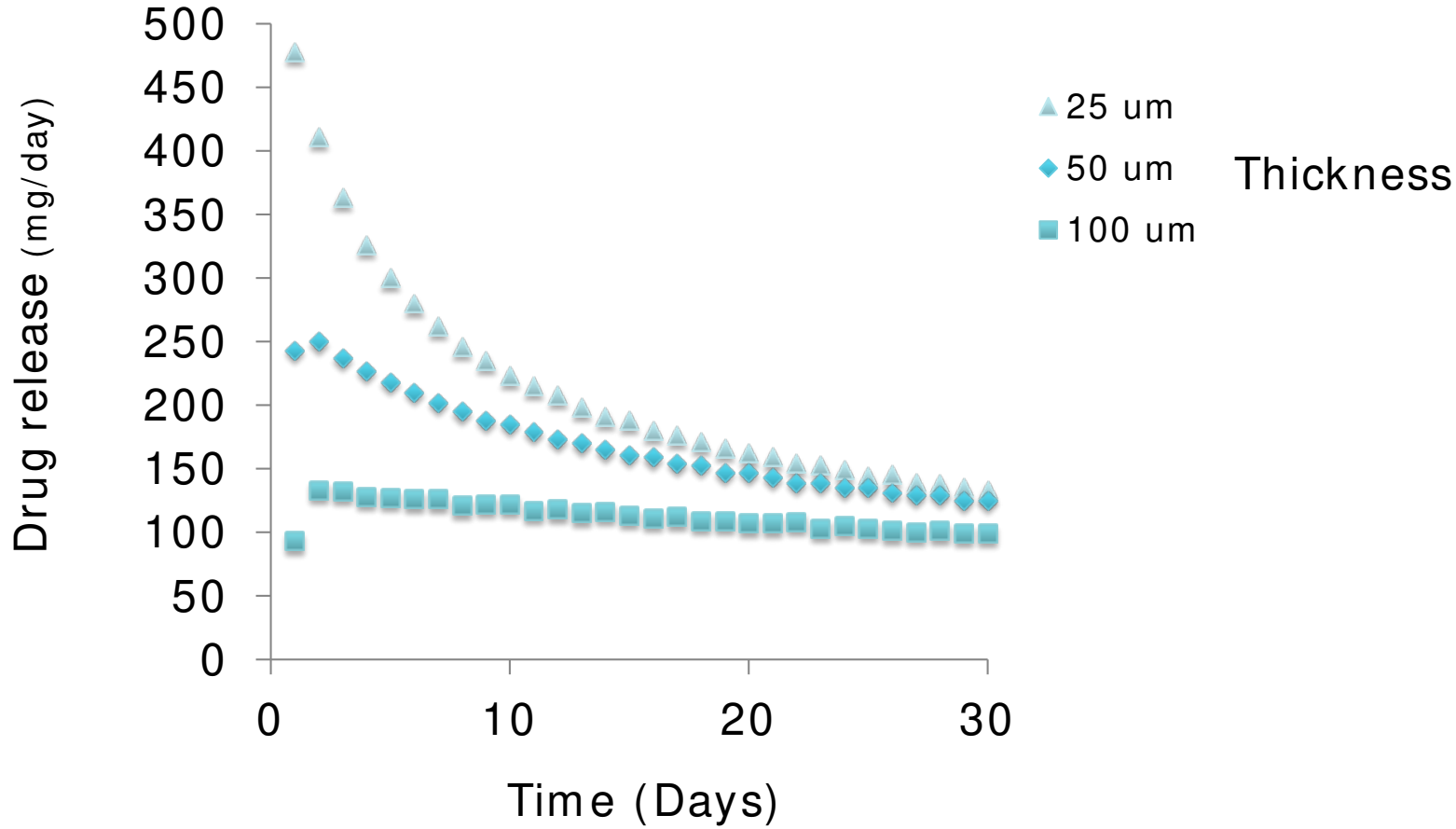




What Dimensions?

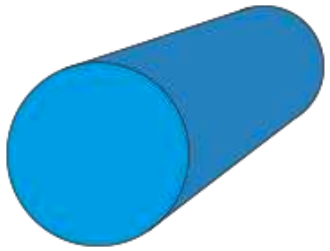
Sheath Thickness Affects Drug Release Rate

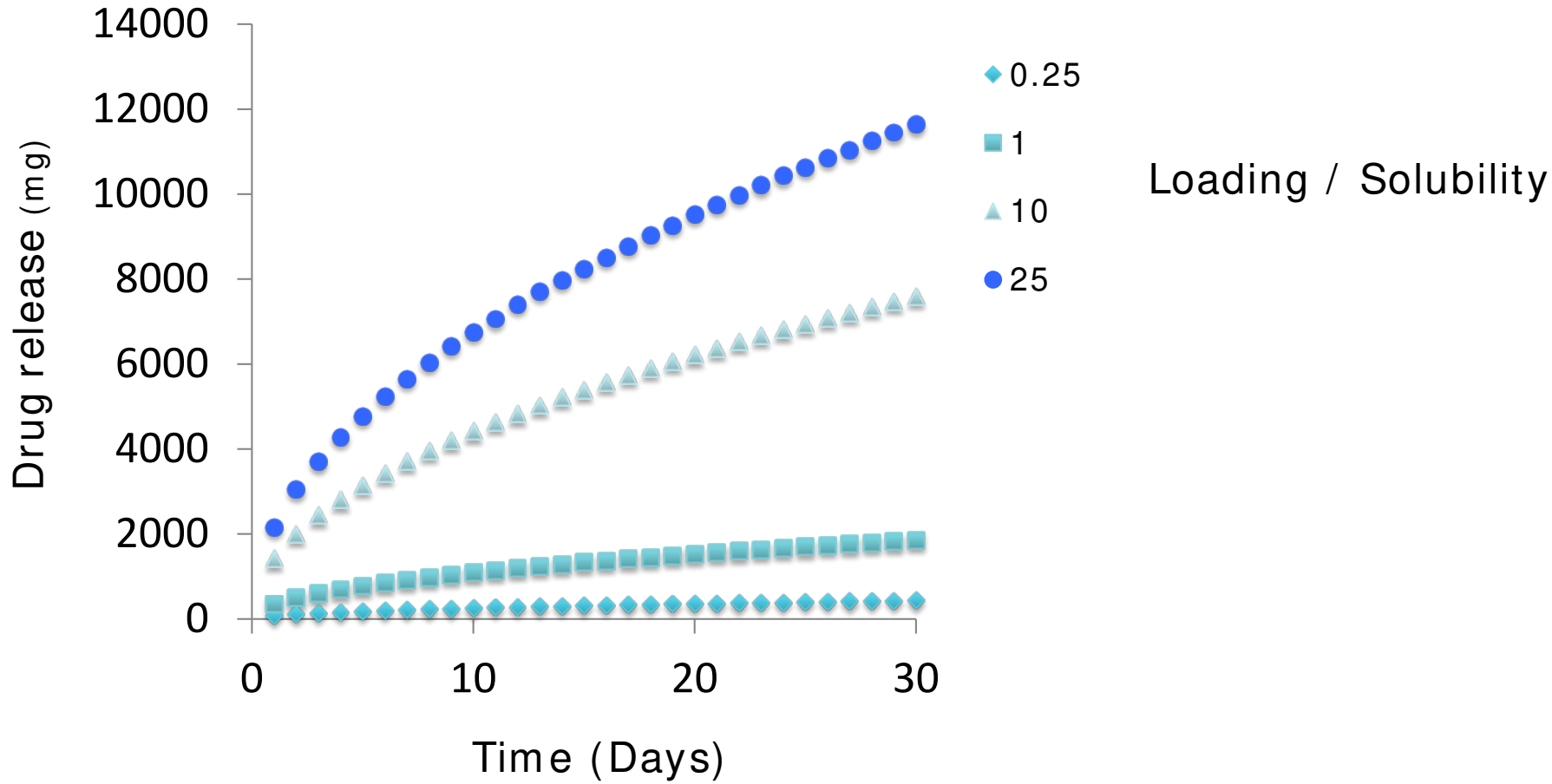




Which Drug Loading?

Drug Loading Affects Release Rate





Which Polymer?

Polymers must be

- Made under cGMP
- Biocompatible
  - ISO10993
  - USP<1031>
  - USP class VI (prolonged mucosal contact)
- Supported by a manufacturer DMF

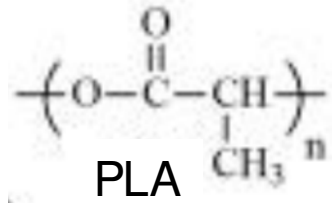
ISO 10993 BIOCOMPATIBILITY TESTS

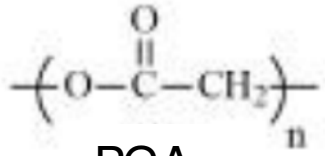
DEVICE CATEGORY			BIOLOGICAL EFFECTS											
Device Type	Body Contact	Contact Duration: Limited ☐ Less than 24 hours; Prolonged ☐ 24 hours to 30 days; Permanent ☐ Over 30 days	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Systemic Toxicity (acute)	Pyrogenicity	Sub-acute and Sub-chronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity
Surface	Skin	Limited	•	•	•								
		Prolonged	•	•	•								
		Permanent	•	•	•								
	Mucosal Membrane	Limited	•	•	•								
		Prolonged	•	•	•								
		Permanent	•	•	•			•	•				
	Breached or compromised surfaces	Limited	•	•	•								
		Prolonged	•	•	•								
		Permanent	•	•	•			•	•				
External Communicating	Blood Path, Indirect	Limited	•	•	•	•	•				•		
		Prolonged	•	•	•	•	•				•		
		Permanent	•	•		•	•	•	•		•	•	•
	Tissue/Bone/ Dentin	Limited	•	•	•								
		Prolonged	•	•	•	•	•	•	•	•			
		Permanent	•	•	•	•	•	•	•	•		•	•
	Circulating Blood	Limited	•	•	•	•	•				•		
		Prolonged	•	•	•	•	•	•	•	•	•		
		Permanent	•	•	•	•	•	•	•	•	•	•	•
Implant	Tissue/Bone	Limited	•	•	•								
		Prolonged	•	•	•	•	•	•	•	•			
		Permanent	•	•	•	•	•	•	•	•		•	•
	Blood	Limited	•	•	•	•	•	•		•	•		
		Prolonged	•	•	•	•	•	•	•	•	•		
		Permanent	•	•	•	•	•	•	•	•	•	•	•

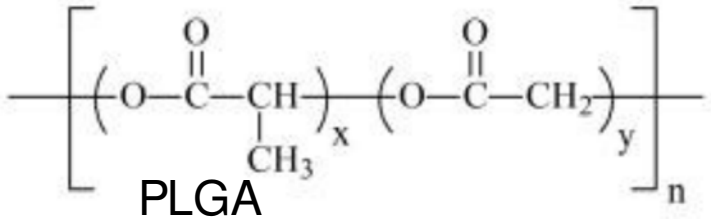
*Additional tests may be required to satisfy FDA requirements

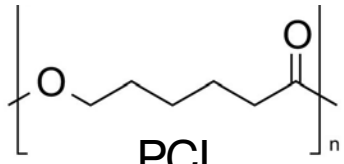
Which Polymer?

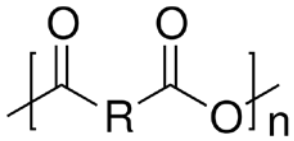
BIORESORBABLE


PLA

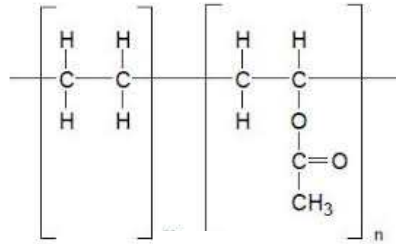

PGA

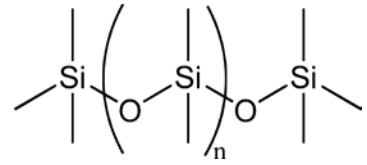

PLGA

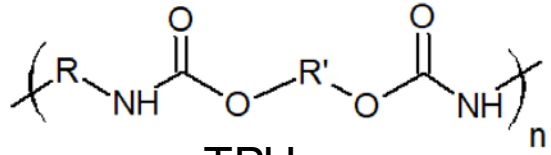

PCL

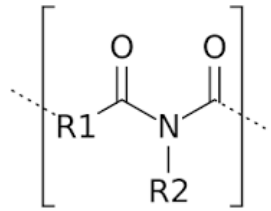

Polyanhydrides

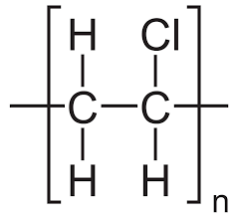
BIODURABLE

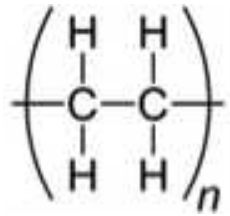

EVA

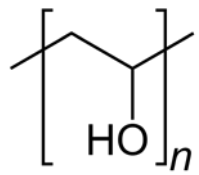

Silicone

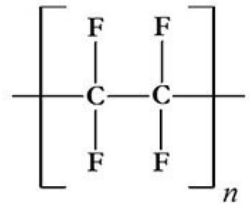

TPU


Polyimide


PVC

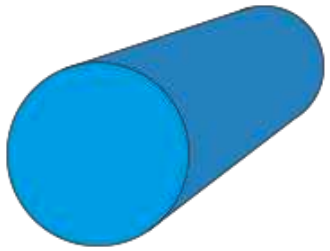

PE

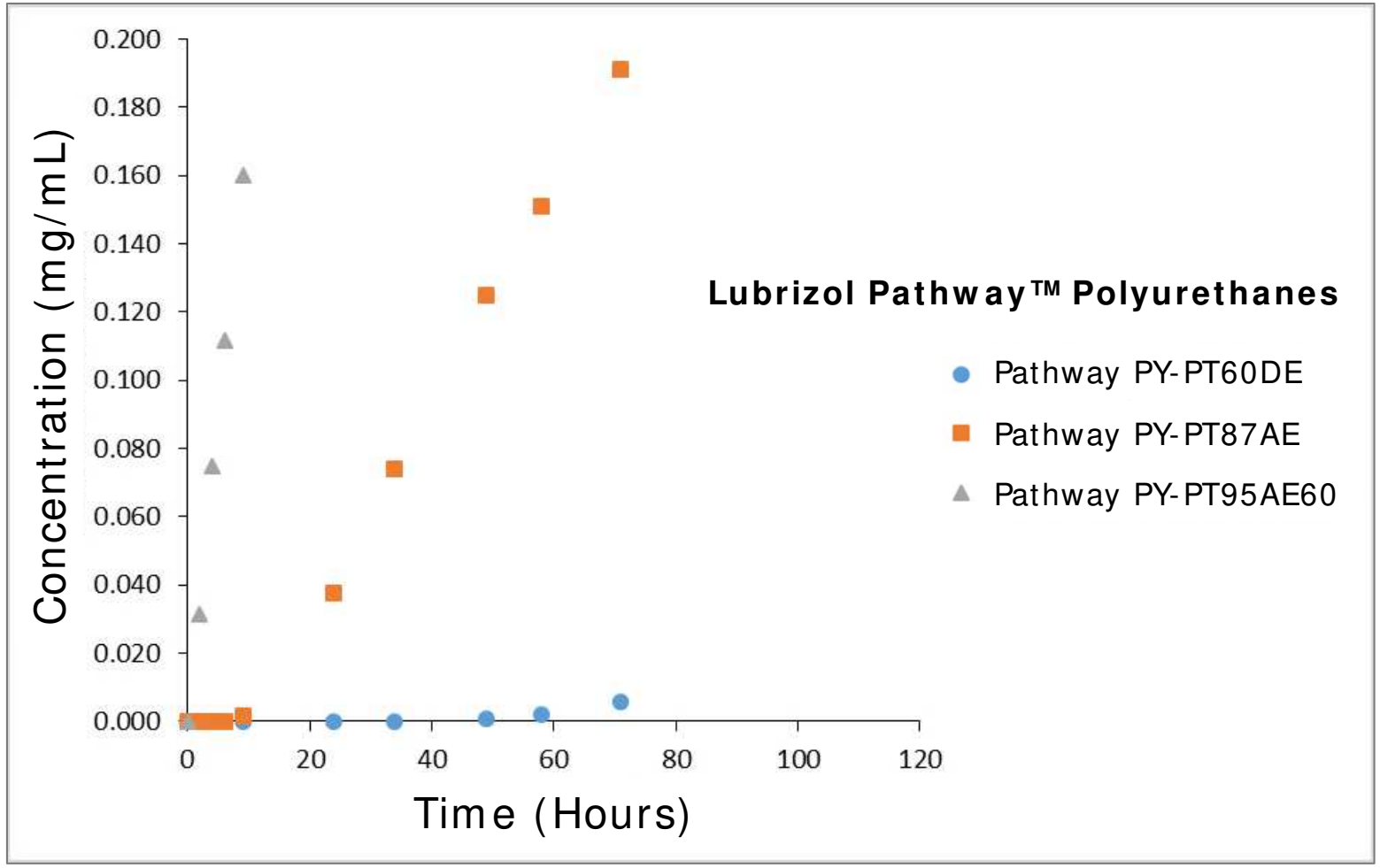

PVA


PTFE

Which Polymer?

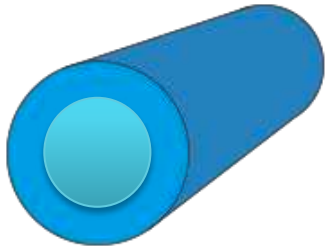
Polymer choice affects drug release rate

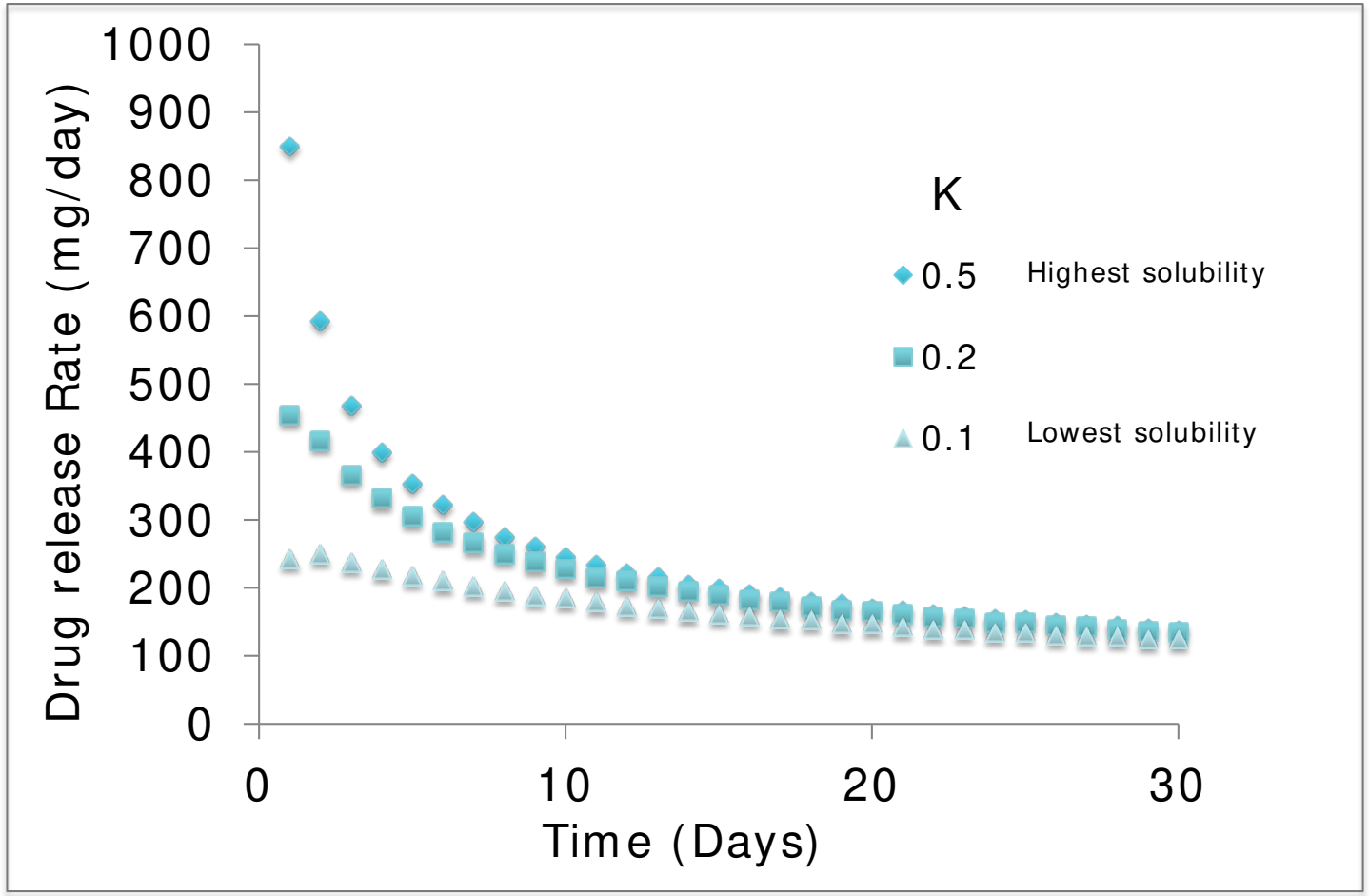




Which Polymers?

Drug Solubility in Core and Sheath Polymers Controls Drug Release Rate

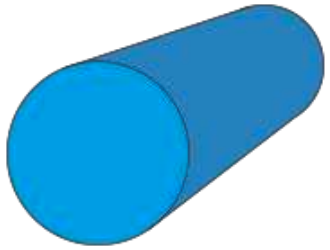


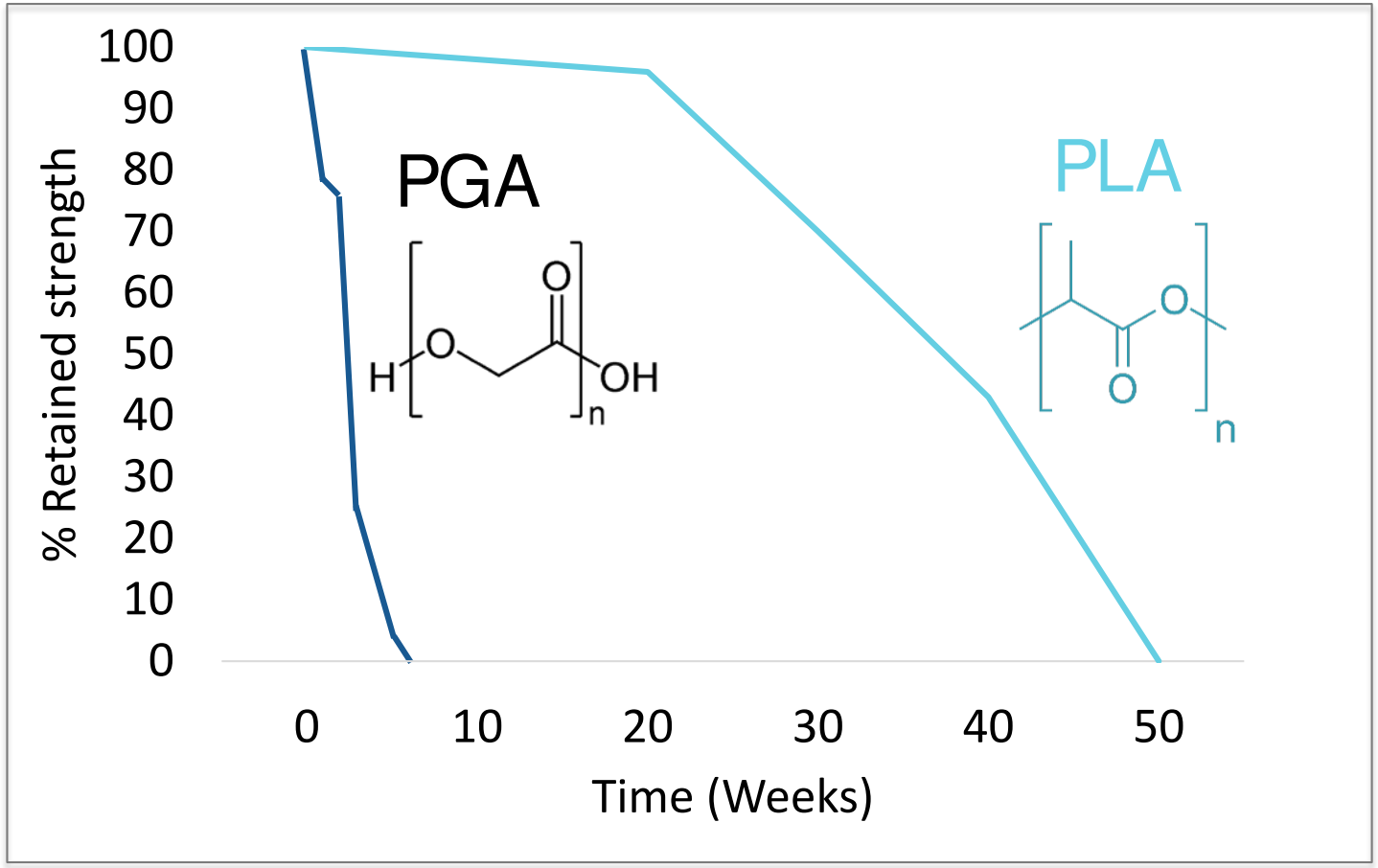


(sheath thickness = 50 um)

Which Polymer?

Polymer Chemistry Affects Degradation Rate (Drug Release Rate)

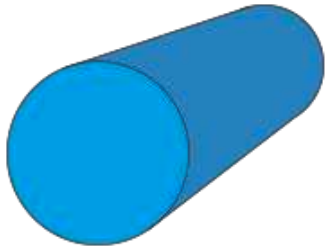


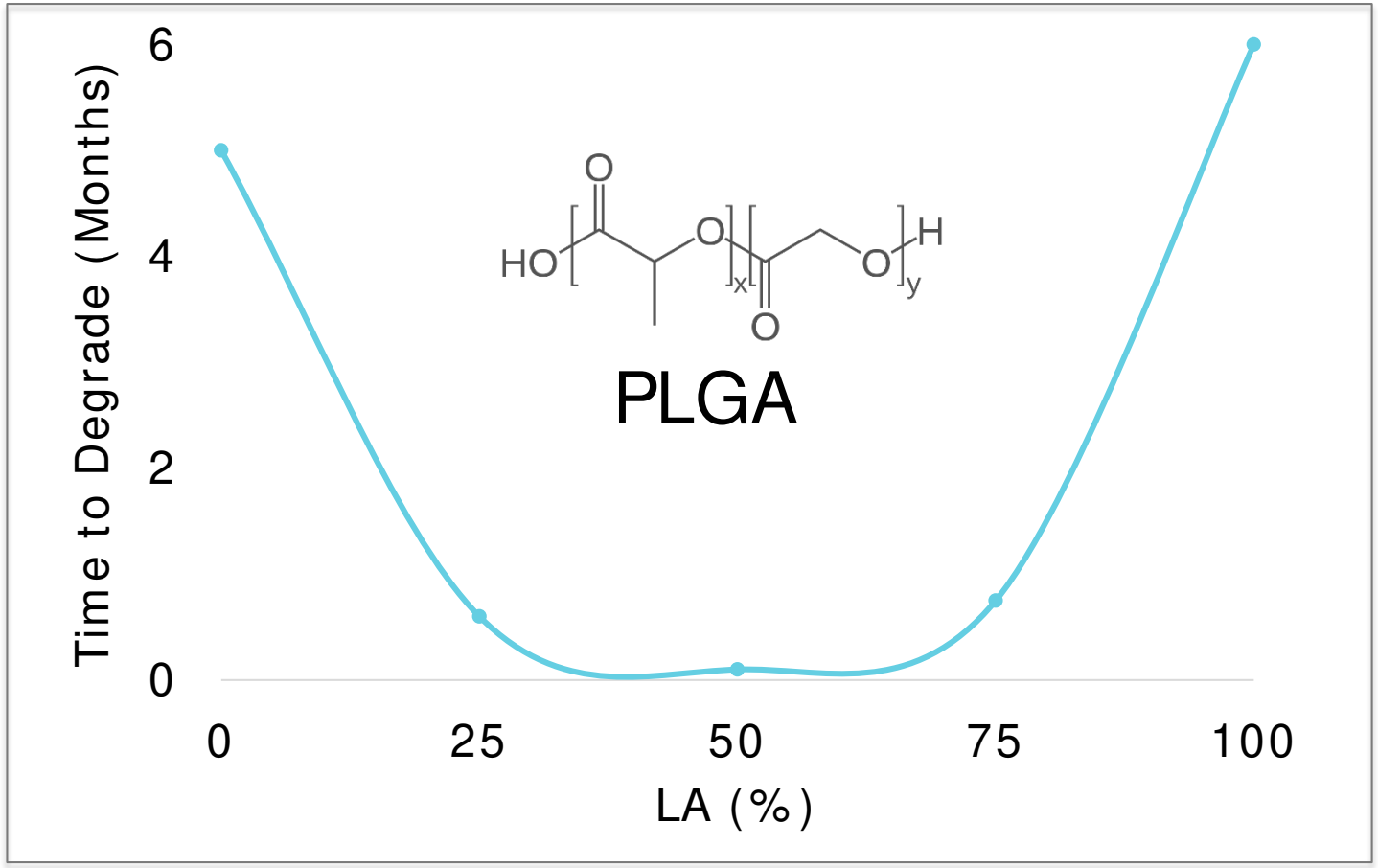


Relative degradation rates: PGA < PLA << PLGA

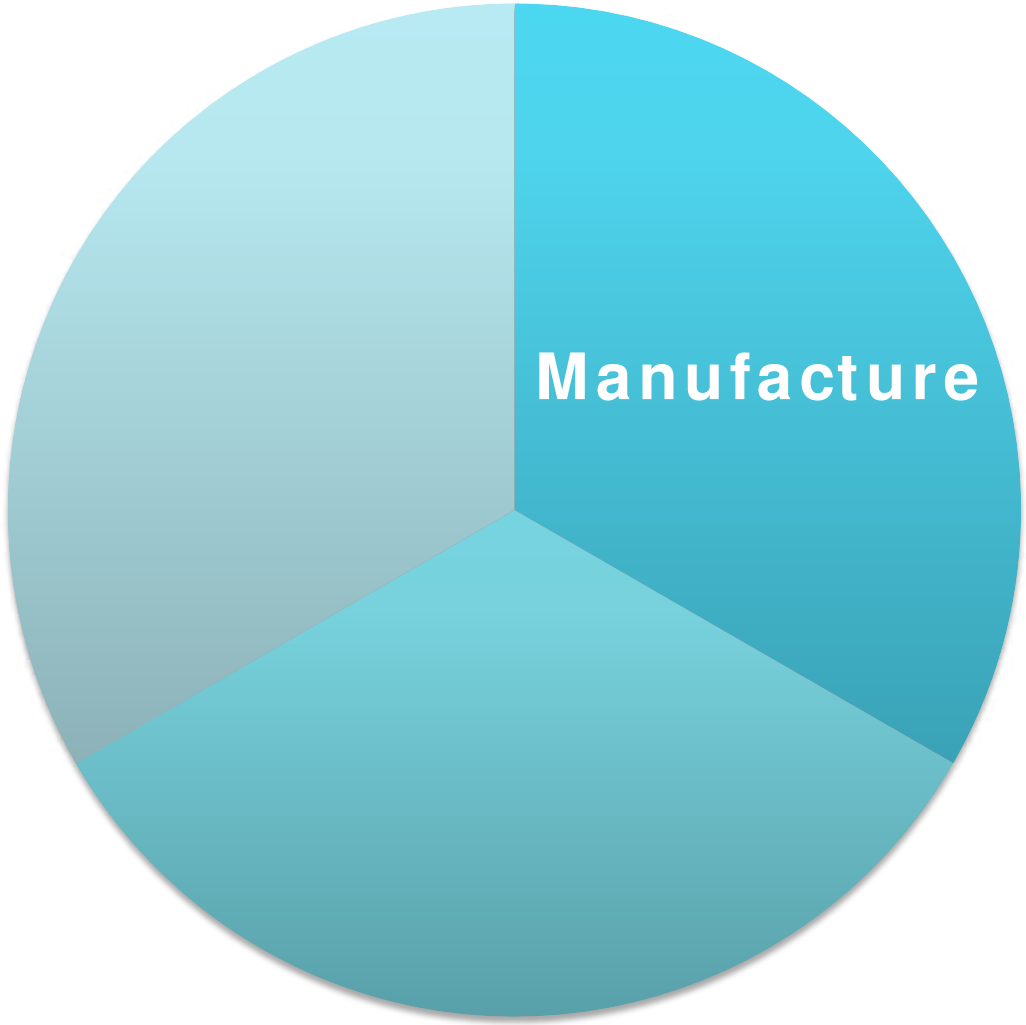
Which Polymer?

Polymer Composition Affects Degradation Rate (Drug Release Rate)





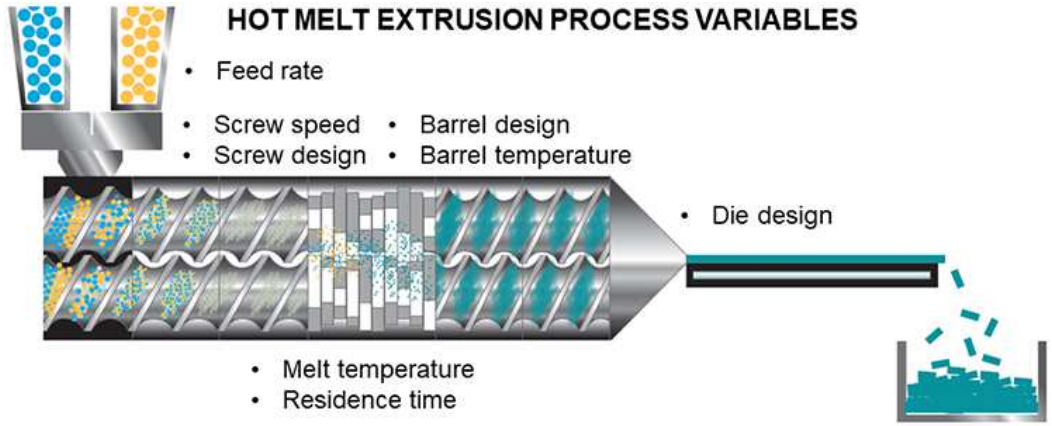
The Key Challenges



How To Mix API in Polymer?

Twin Screw Hot Melt Extrusion

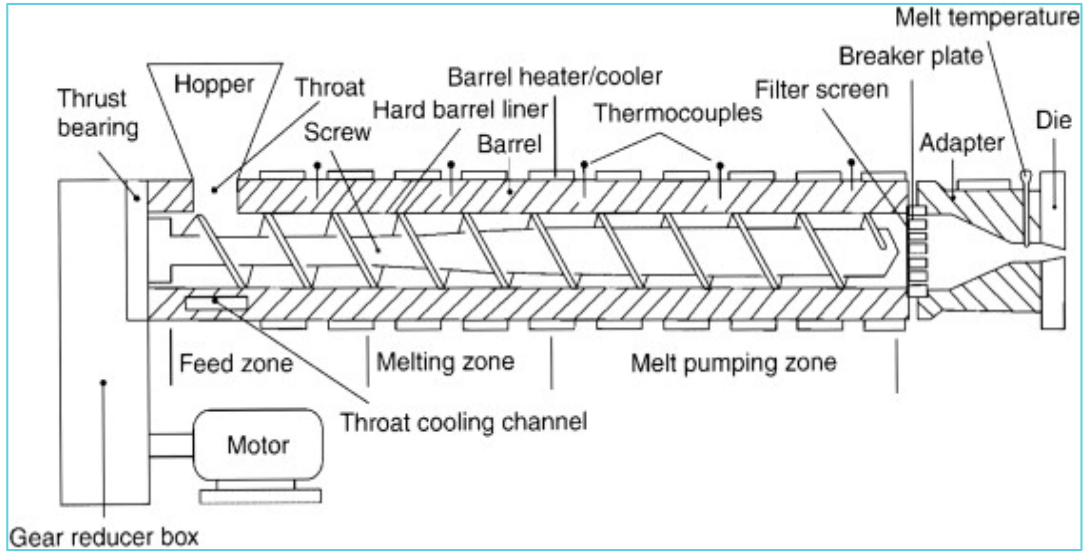
Feeder(s)

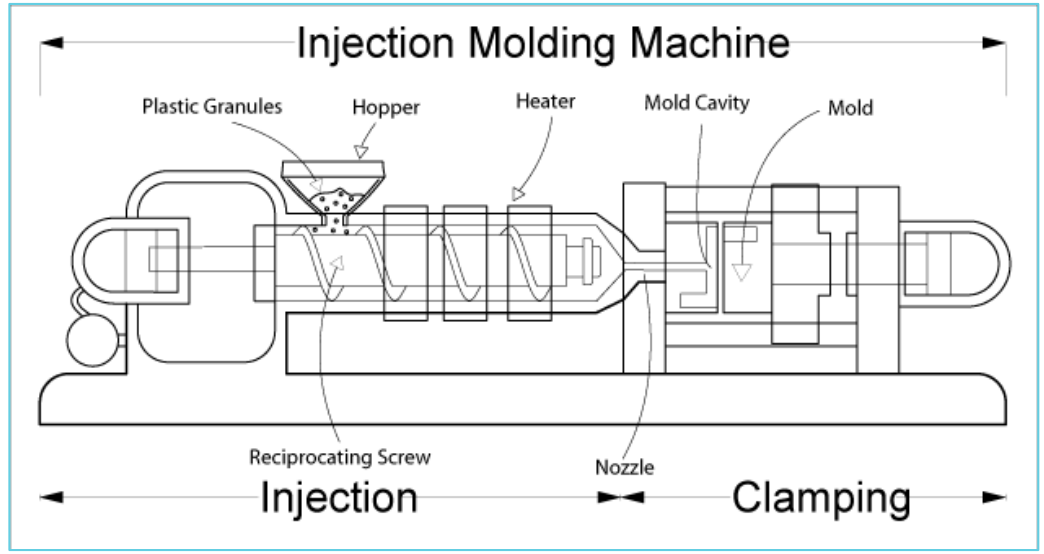


Barrel containing screws

Photo courtesy of Lestritz.

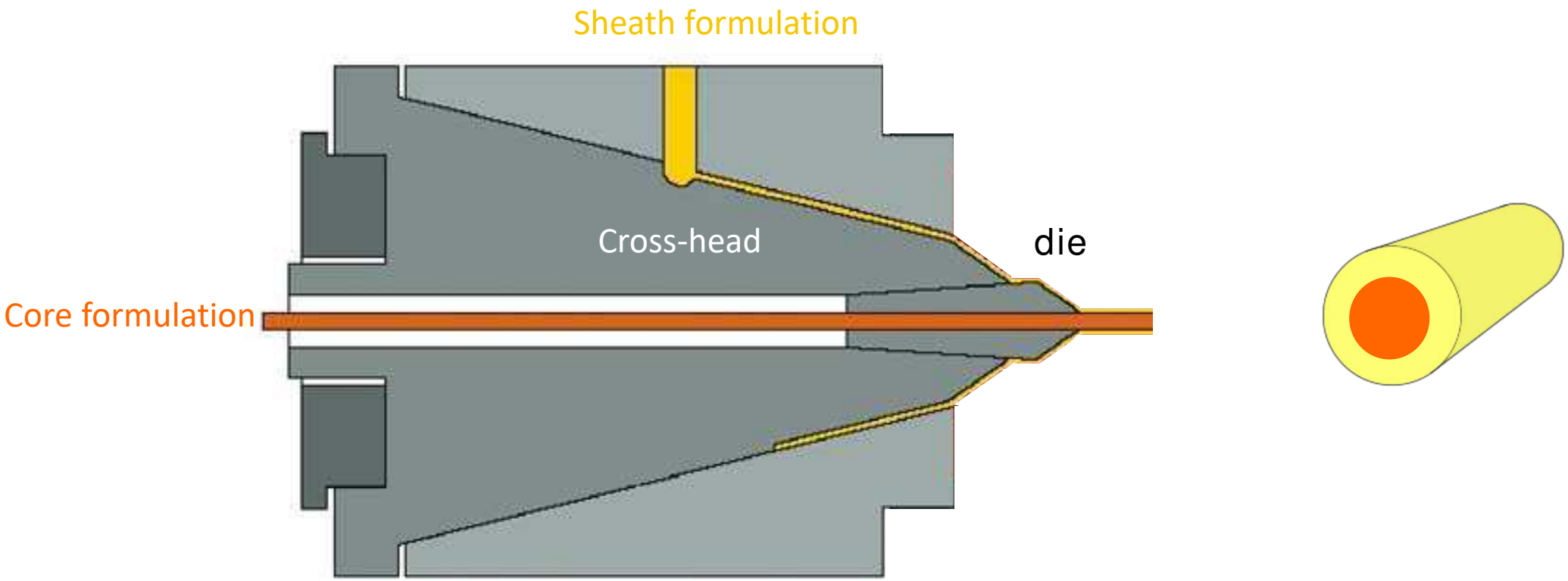
How To Make Matrix Implants?





	EXTRUSION	INJECTION MOLDING
Process	Continuous	Batchwise
Output	Rods or tubes (catheters)	“Any" form factor
Throughput	Limited by barrel dimensions and flow rates	Limited by mold cavity number and cycle time
Cost	Relatively Inexpensive Custom dies Requires cutting machine	Relatively inexpensive Potentially expensive molds
Other		Sprue residues?

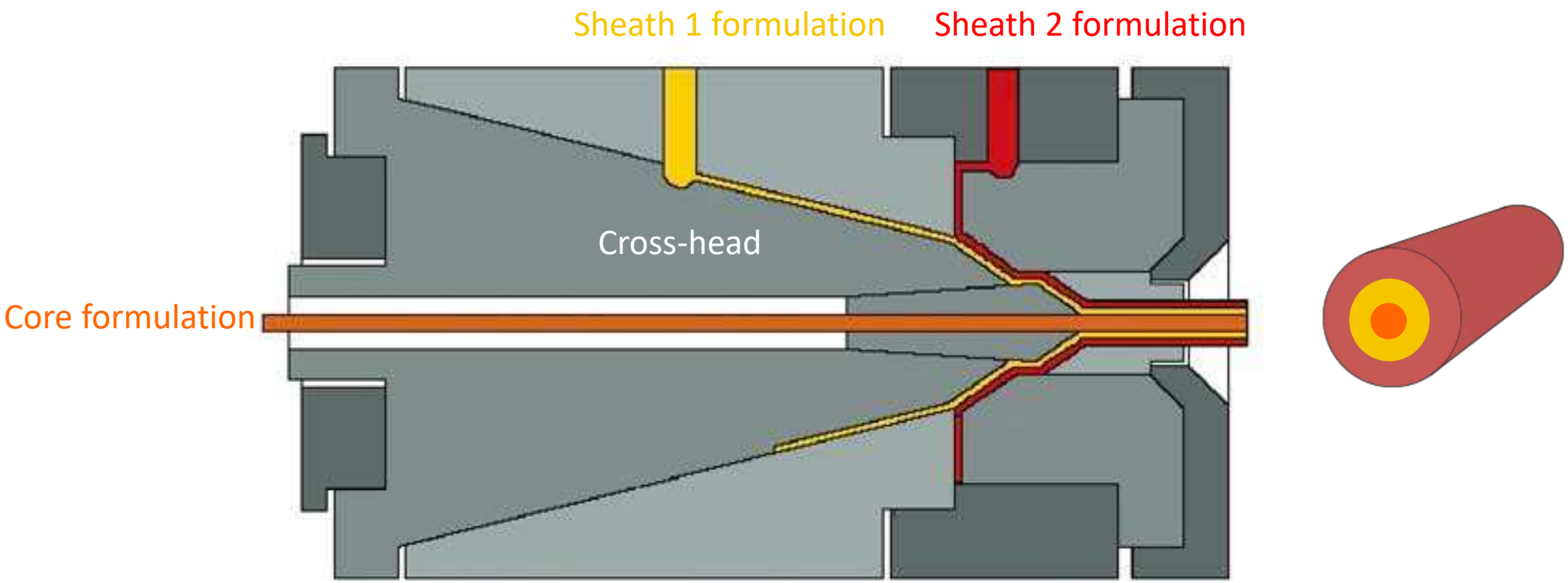
How To Make Reservoir Implants?
1. Core Sheath



Continuous process

Requires two single screw extruders

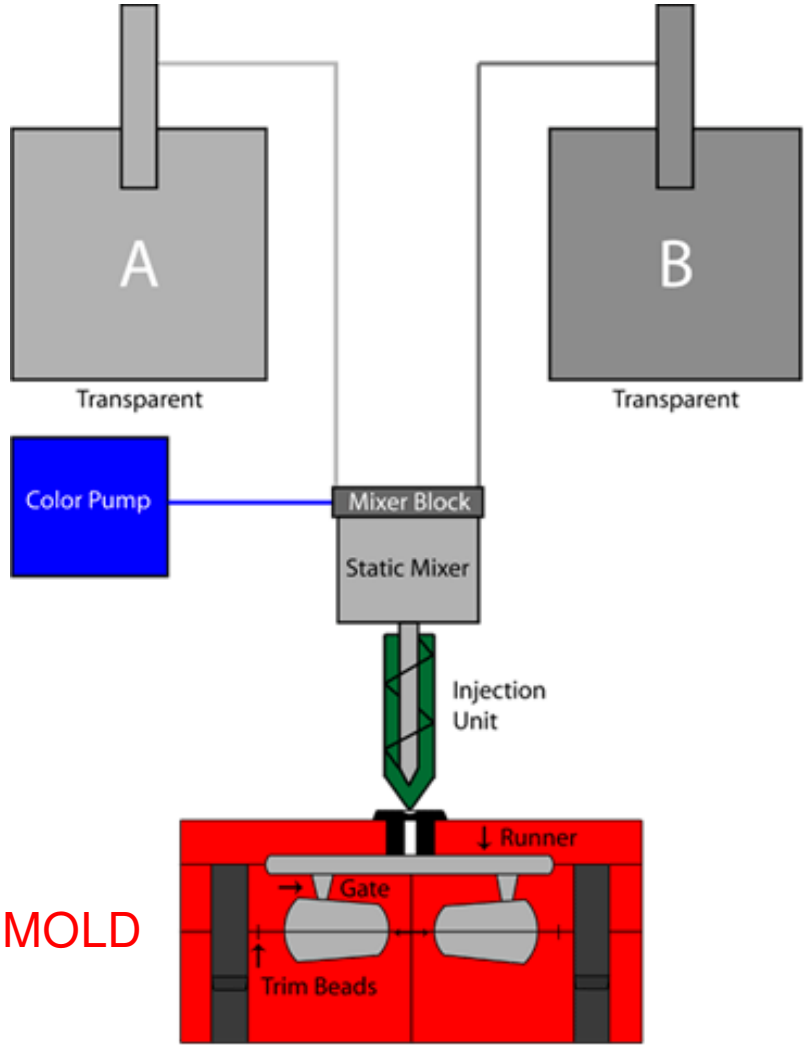
How To Make Reservoir Implants?
2. Core Sheath-sheath



Continuous process

Requires two single screw extruders

How To Make Silicone Implants?



- API in one or both liquid prepolymers (A & B)
- Chemically cure in mold cavities (heat)
  - API stability?
- Requires Sn or Pt catalyst
  - API compatibility?
- Slow batch process (cure takes time)
- Potential for ethanol evolution

How to Manufacture With Limited Materials?

Options:

- Solution casting
- Powder mixing and small scale thermal forming

Turbula mixer
(API + polymer)

Mini twin screw extruder
(10 mm screw, 10g batch)

Vacuum compression molder

Mini injection molder

The Key Challenges

in vitro Drug Release Testing (IVRT)

- Measure of drug release in a controlled laboratory environment

- Test must be **representative, sensitive, and reproducible**
  - Medium that reflects *in vivo* conditions
  - Selection of appropriate stirring/soaking procedure
  - Importance of identifying and maintaining sink conditions
  - Proper sampling frequency
  - Proper test duration

in vitro Drug Release Testing (IVRT)

IVRT is Good for:

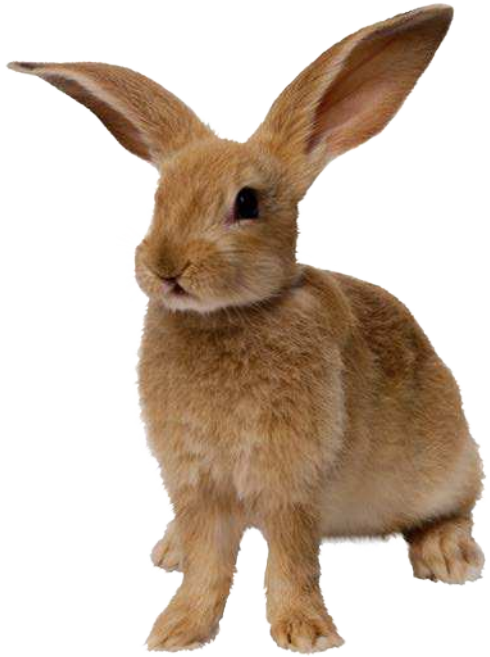
- ✓ Assessing effects of materials and design choices
- ✓ Estimating timeframe of drug release
- ✓ Predicting long term release from “short” term data
- ✓ Developing / refining / validating implant models
- ✓ Batch release testing

LUBRIZOL LIFE SCIENCE

in vitro Drug Release Testing (IVRT)

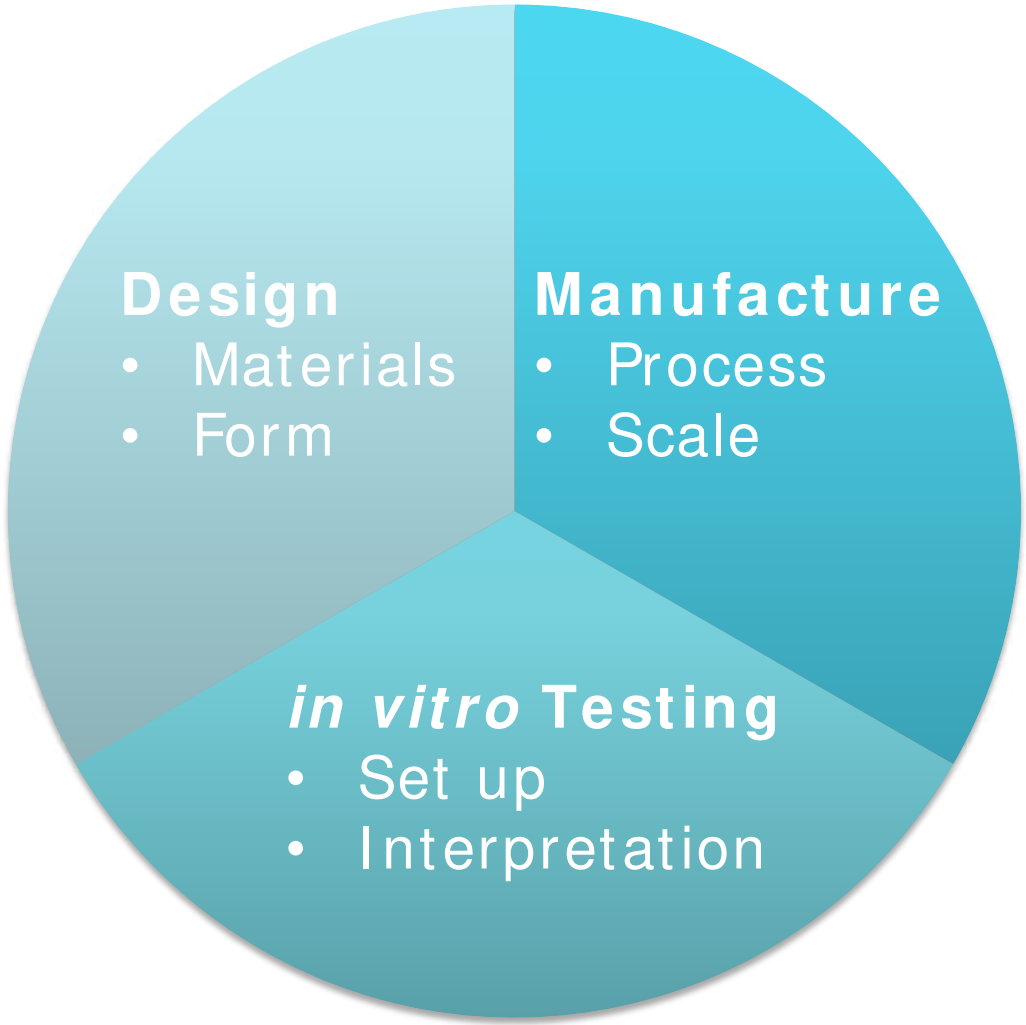
IVRT is **NOT** good for predicting *in vivo* performance

- Use IVRT wisely
- Go *in vivo* ASAP!



Implant Challenges Summary

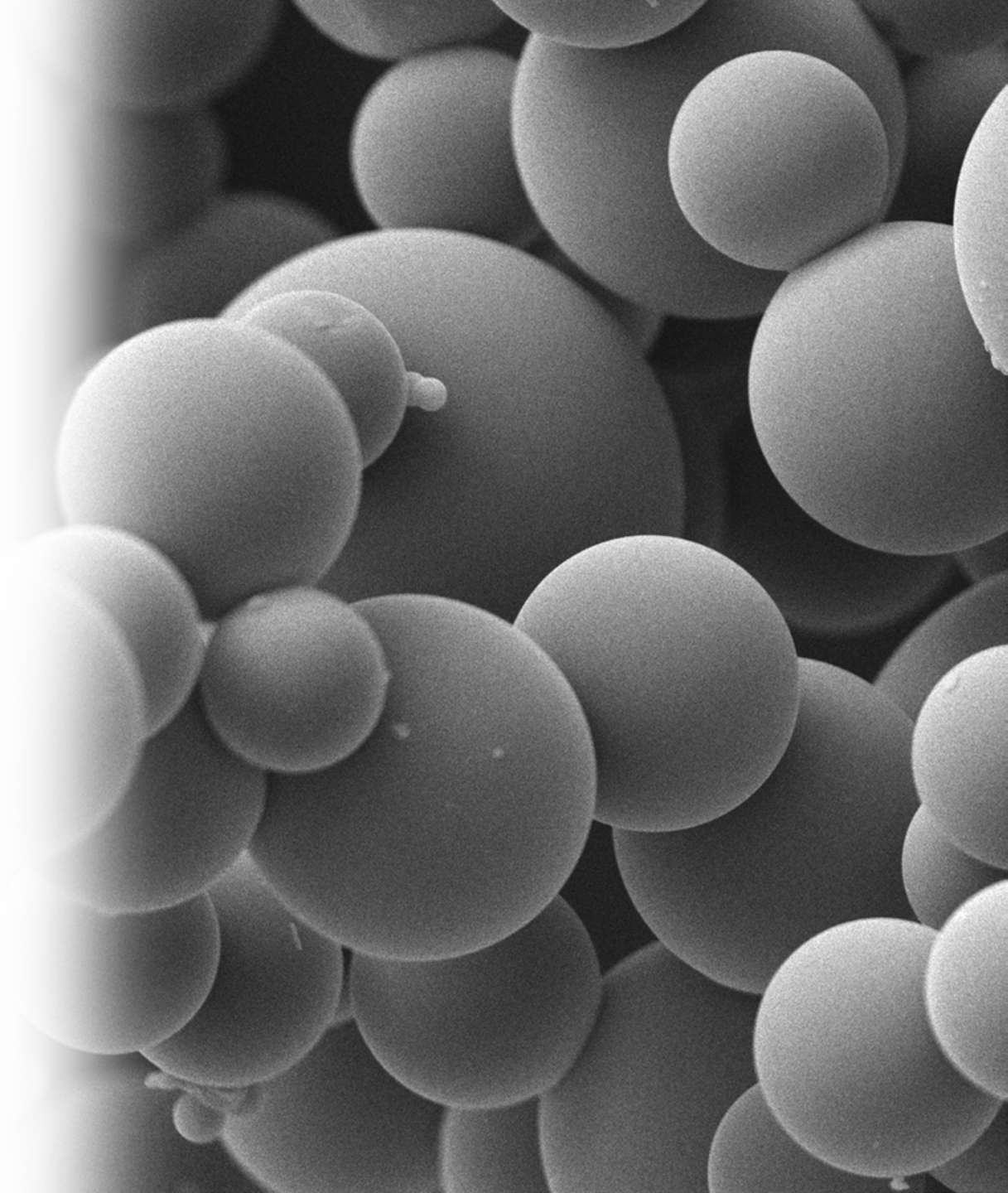
Successful implant development depends on properly addressing the challenges of:



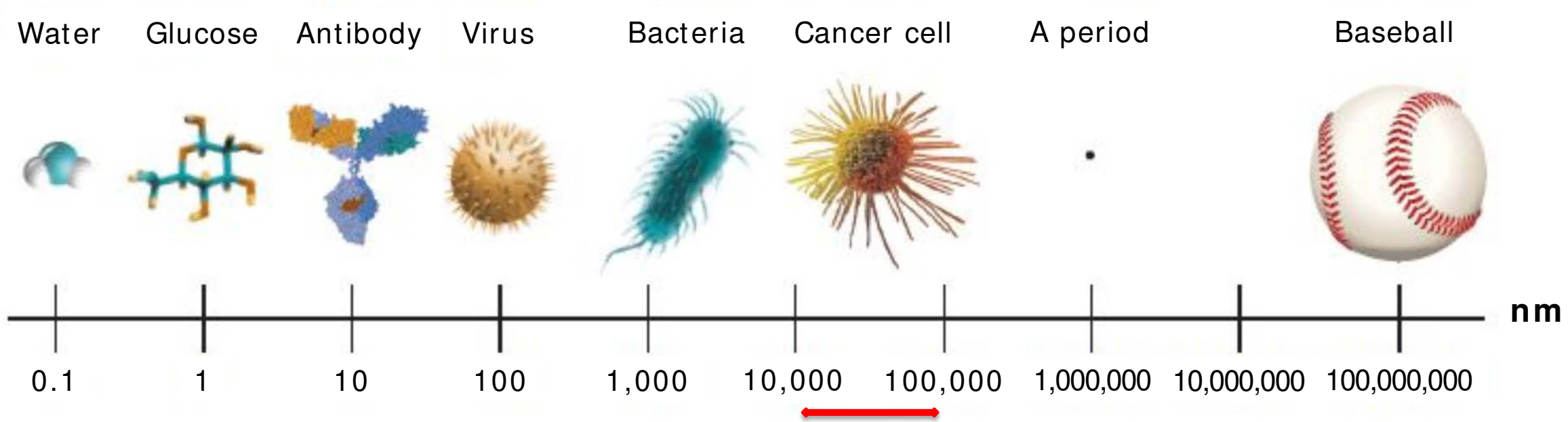
Part 2

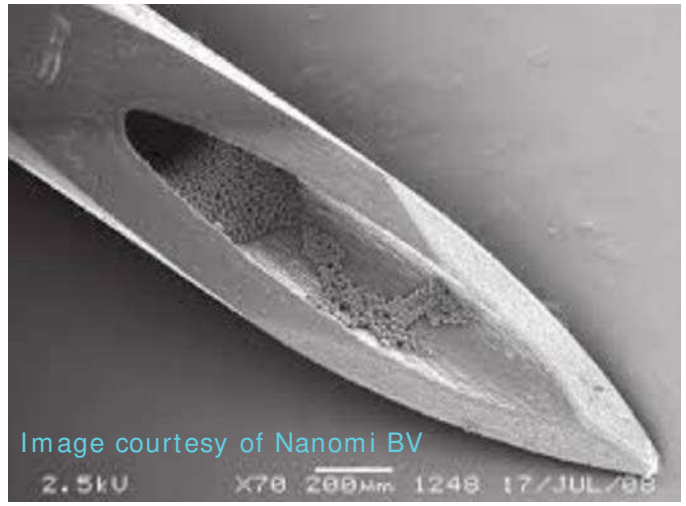
Bioresorbable (Microparticle) Depots

HEALTH

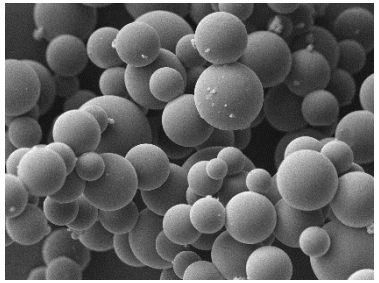


What Size are Microparticle Depots?





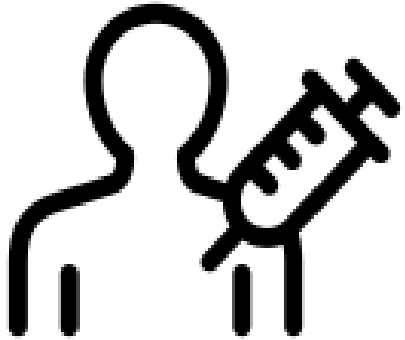
Depot Features



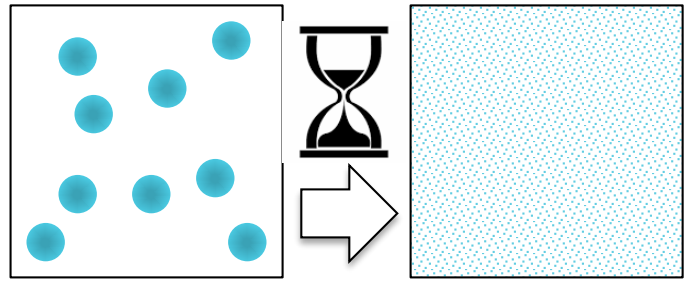
Solid microspheres

Dry powders (reconstitution)

Sterile

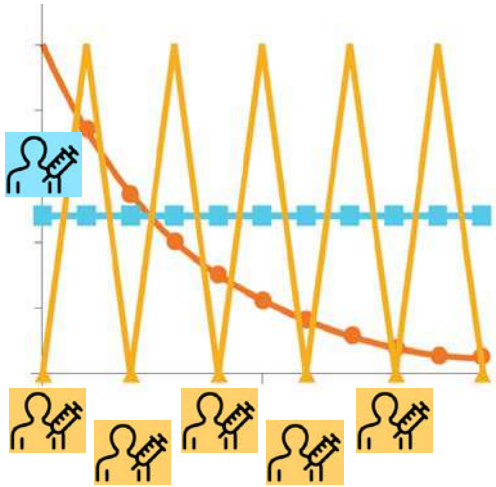


Parenteral ROA

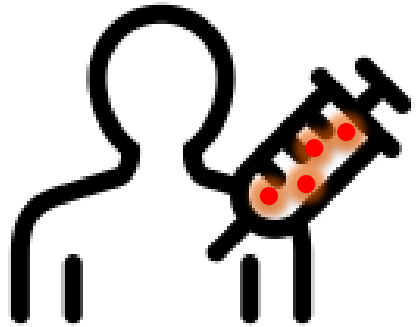


Degrade completely (~ months)

Why Microparticle Depots?



Reduced dose frequency
prolonged delivery
(patient compliance)



Accurate delivery
of small quantities
of potent drugs

Protection
of labile APIs

Avoids first-pass
degradation

Sustained and **Controlled** delivery of an API over long periods of time

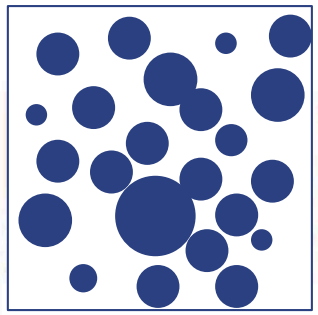
Key Challenges

- Some challenges same as with resorbable implants
  - Which polymer?
  - Ensuring API stability with polymer degradants
  - Which sterilization process?

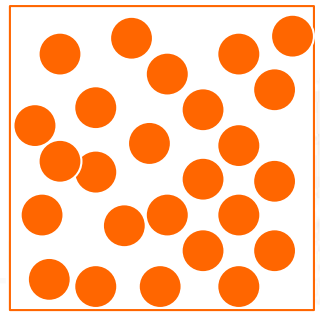
- And some new ones…
  - What particle size (distribution)?
  - What manufacturing process?
  - How to preventing agglomeration?
    - During production
    - During lyophilization
  - How to handle residual solvents
  - How to conduct IVRT with microparticles

What Particle Size & Distribution?

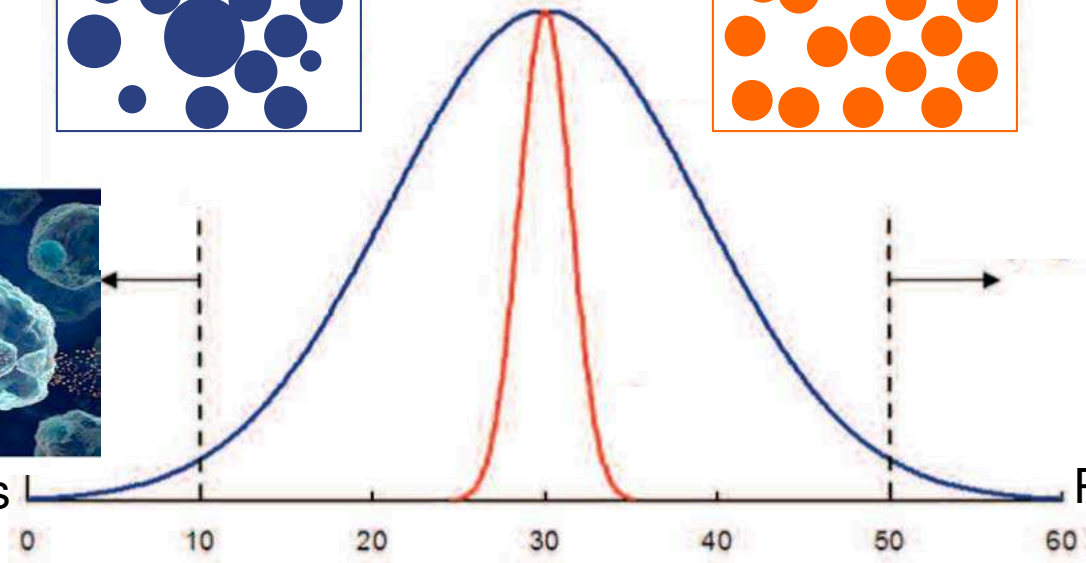
Polydisperse



Monodisperse



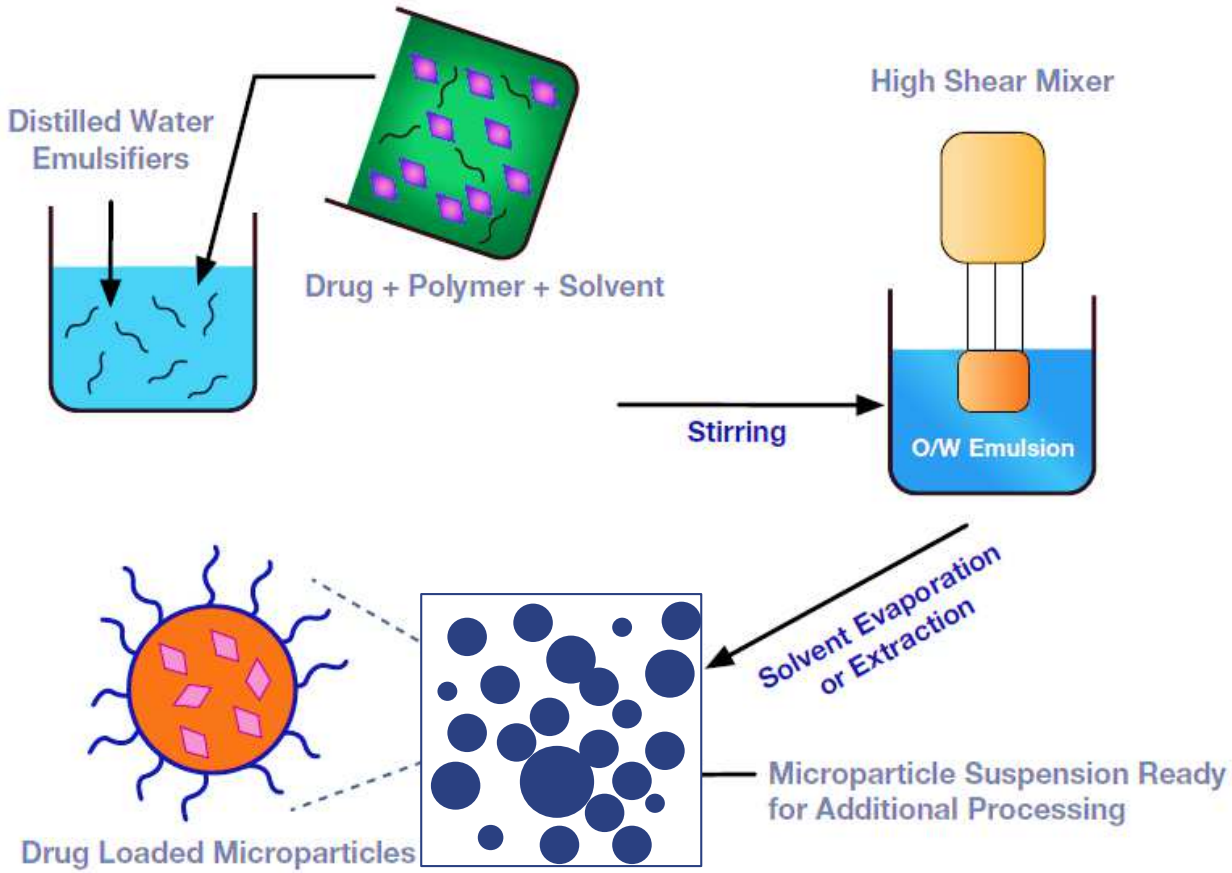
Phagocytosis



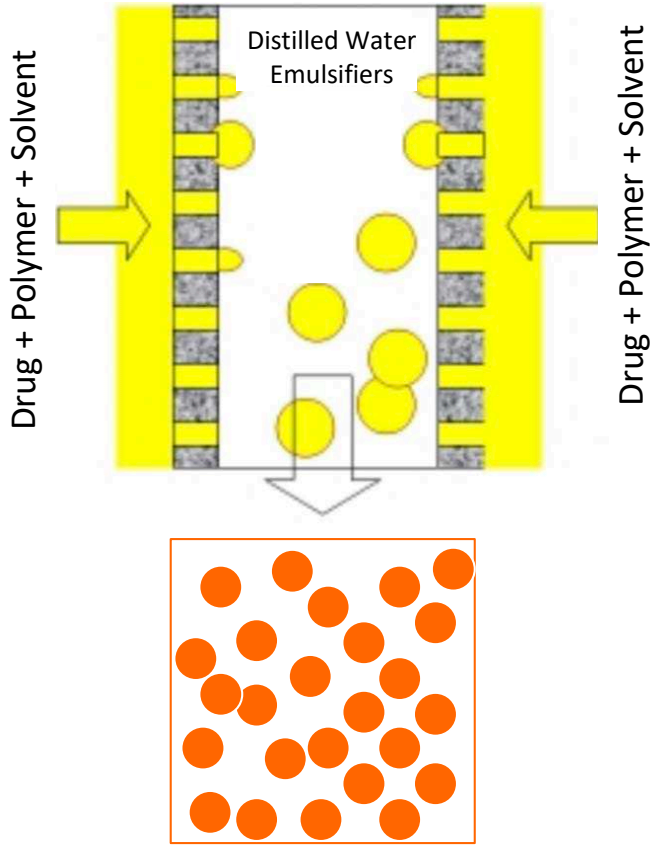
Poor syringe-ability

What Manufacturing Process?

Emulsification / Evaporation



Membrane Emulsification



How To Prevent Particle Agglomeration?

During Production

- Correct choice of emulsifier (polymers)
- Correct choice of solvent
- Optimum mixing time
- Optimum solvent removal protocol

During Lyophilization

- Correct Choice of lyoprotectant (sugars)
- Proper lyophilization cycle development

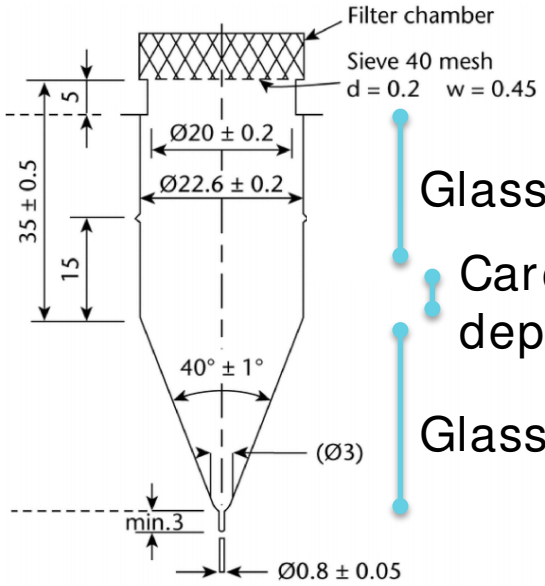
How to Handle Residual Solvents?

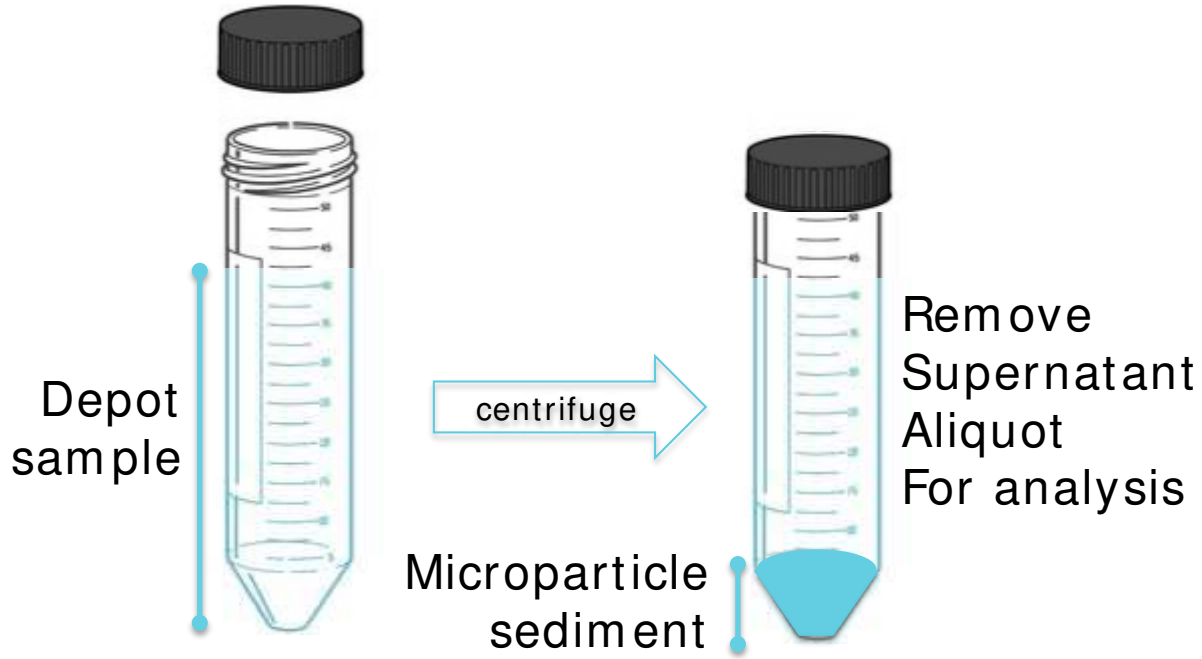
- ICH guideline Q3C (R7) on impurities: guideline for residual solvents
- Places residual solvents in three classes:
  - ***Class 1 solvents: Solvents to be avoided***
    - Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
  - ***Class 2 solvents: Solvents to be limited***
    - Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity.
    - Solvents suspected of other significant but reversible toxicities.
  - ***Class 3 solvents: Solvents with low toxic potential***
    - Solvents with low toxic potential to man; no health-based exposure limit is needed.
    - Class 3 Solvents have PDEs of 50 mg or more per day.

ICH Guidelines explicitly state which solvents fall into each category

How to Handle Microparticles In IVRT?

Apparatus 4
(USP<711>)





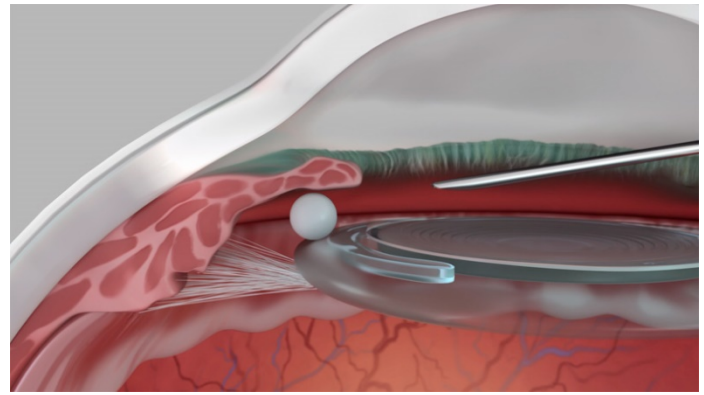
- Standardized compendial apparatus
- Flexible configuration
  - open loop mode (eluent to waste) for poorly soluble drugs
  - closed loop (eluent recycled through cell) for better sensitivity
- Auto-sampling and in-line detection possible

- Inexpensive
- Potentially higher throughput

Case Study: Microparticle Formulation and Characterization

- **Goal**: Preparation and characterization of API loaded microparticle depot formulations

- **Study Design:**
  - **Polymers**: Different grades of PLGA (lactide:glycolide ratio and MW)
  - **API**: Dexamethasone (widely used corticosteroid with anti-inflammatory and immunosuppressant properties)
  - **Particle properties**: Measure particle size distribution and in vitro release



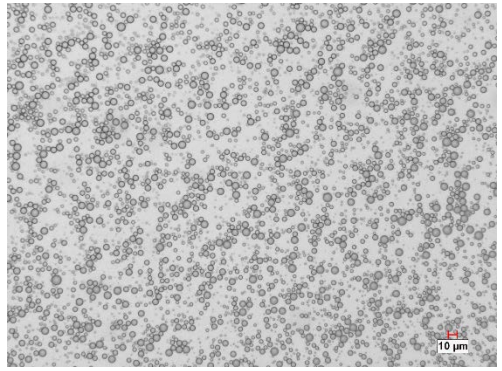
DEXYCU® Depot
(Dexamethasone intraocular suspension)

Case Study: Materials and Methods

- **Polymers**
  - PLGA 50:50 (Lactide:Glycolide); Inherent viscosity 0.2 dL/g
  - PLGA 75:25 (Lactide:Glycolide); Inherent viscosity 0.2 dL/g
- **API**
  - Dexamethasone; target loading ~20% w/w particle
- **Manufacturing Methods**
  - Emulsion/solvent evaporation approach using:
    - Dip-style (batch) homogenizer
    - In-line (continuous process) homogenizer
    - Micropore/microfluidic process

Case Study: Characterization

Property	Test Method
Appearance	Optical Microscopy
Particle Size Distribution	Laser Diffraction
Assay	HPLC
In Vitro Release Testing – accelerated	USP Apparatus IV



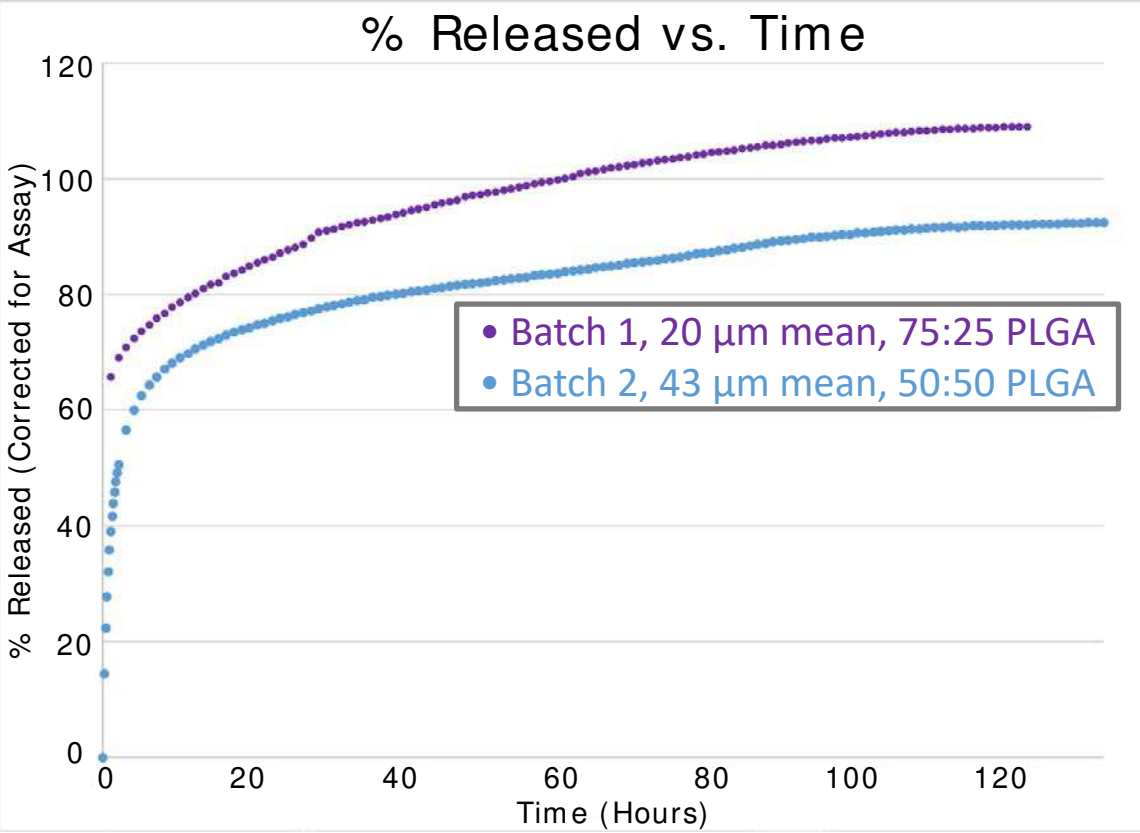
Optical microscopy of PLGA microparticles

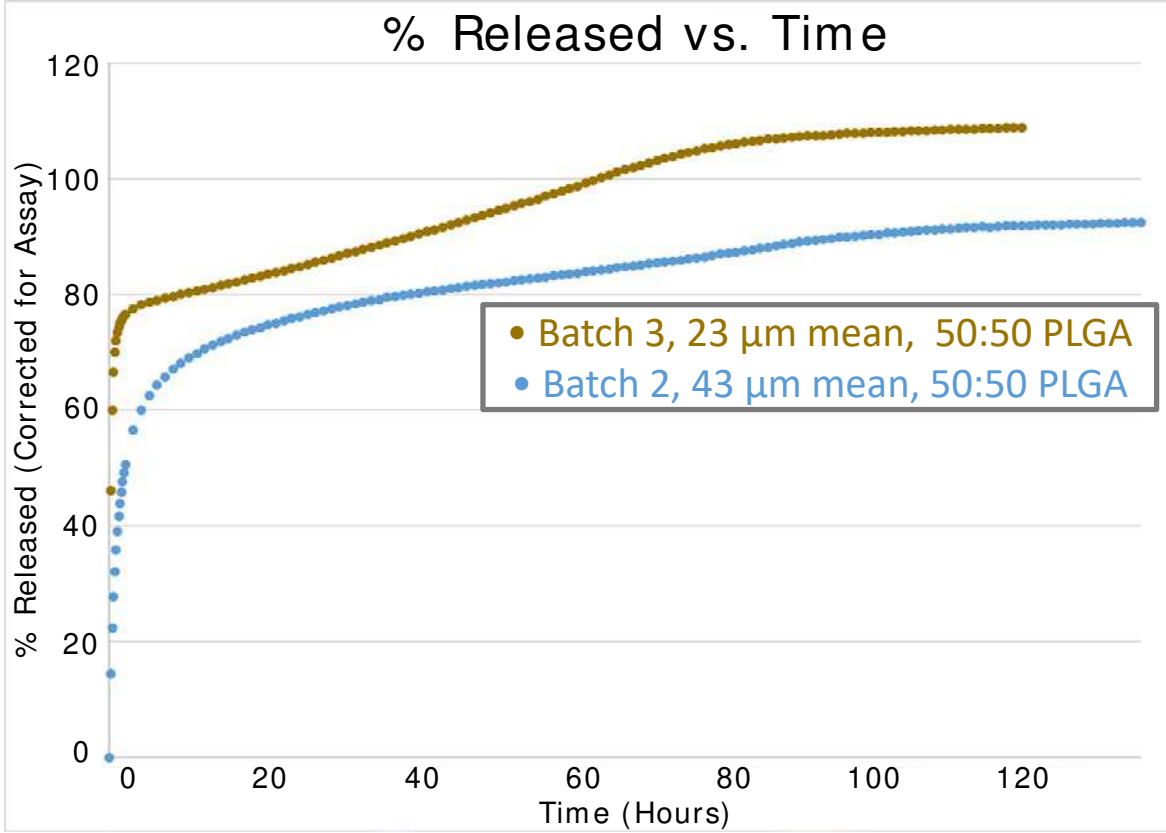
USP apparatus IV

Case Study: Particle Properties

	BATCH 1	BATCH 2	BATCH 3
Polymer	75:25 PLGA	50:50 PLGA	50:50 PLGA
Polymer IV	0.2 dL/g	0.2 dL/g	0.2 dL/g
Process	Batch homogenization	Batch homogenization	Micropore
Mean Particle Size	20.3 µm	43.4 µm	22.9 µm
Drug Loading	22.5% w/w	21.5%	17.3%

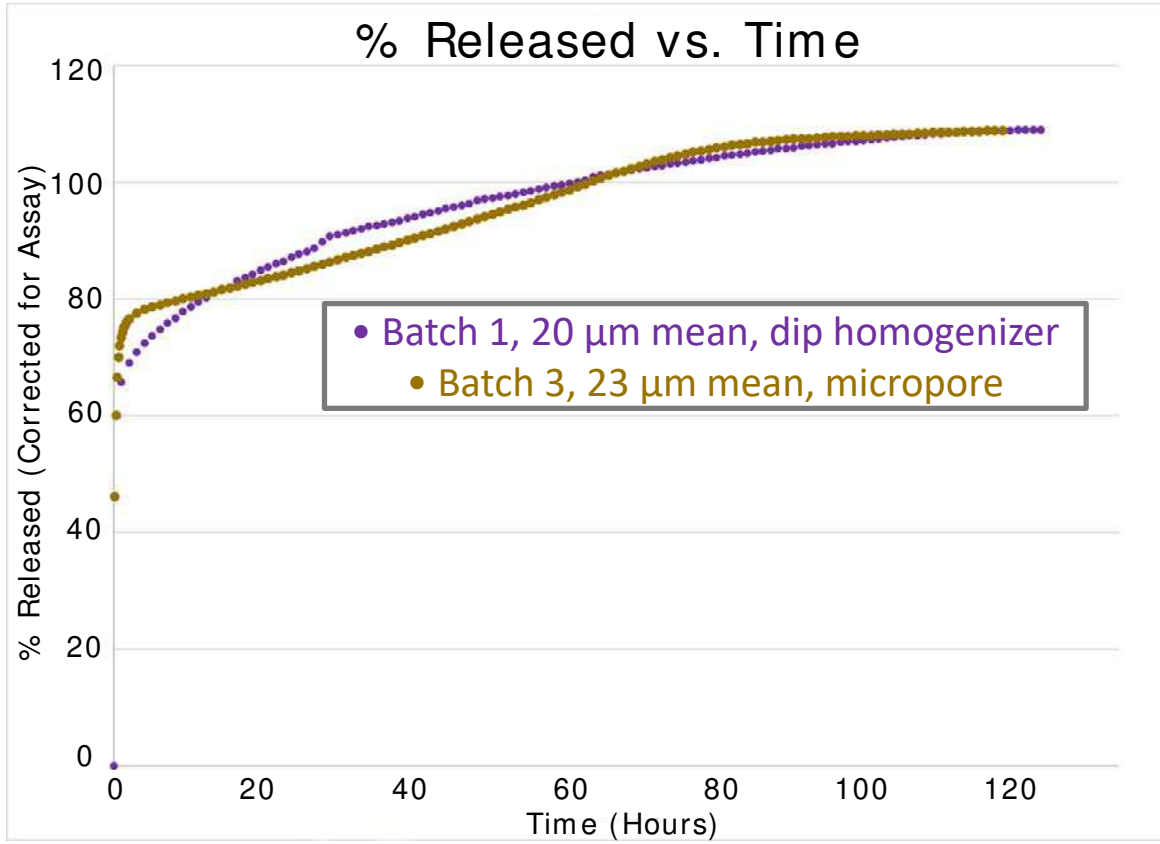
Case Study: *In Vitro* Release Testing





The greatest difference in mean particle size led to the greatest difference in release profiles.

Case Study: *In Vitro* Release Testing



Different manufacturing methods led to similar mean particle sizes and release profiles.

Microparticle Depot Summary

- Desired dosing features:
  - Sustained and controlled delivery of APIs
- Challenges:
  - Particle size, materials selection, residual solvents, release rate, agglomeration
- Success achieved by:
  - Formulation design, manufacturing execution and analytical expertise

Overall Summary: Implants and Depots

- Many advantages and new product opportunities

- Complex development, requiring:
  - Specialized equipment
  - Materials and design choices
  - Careful use of IVRT
  - Experienced, expert team

The Health business of Lubrizol Life Science is your partner for implant and depot development/manufacturing.

Questions?

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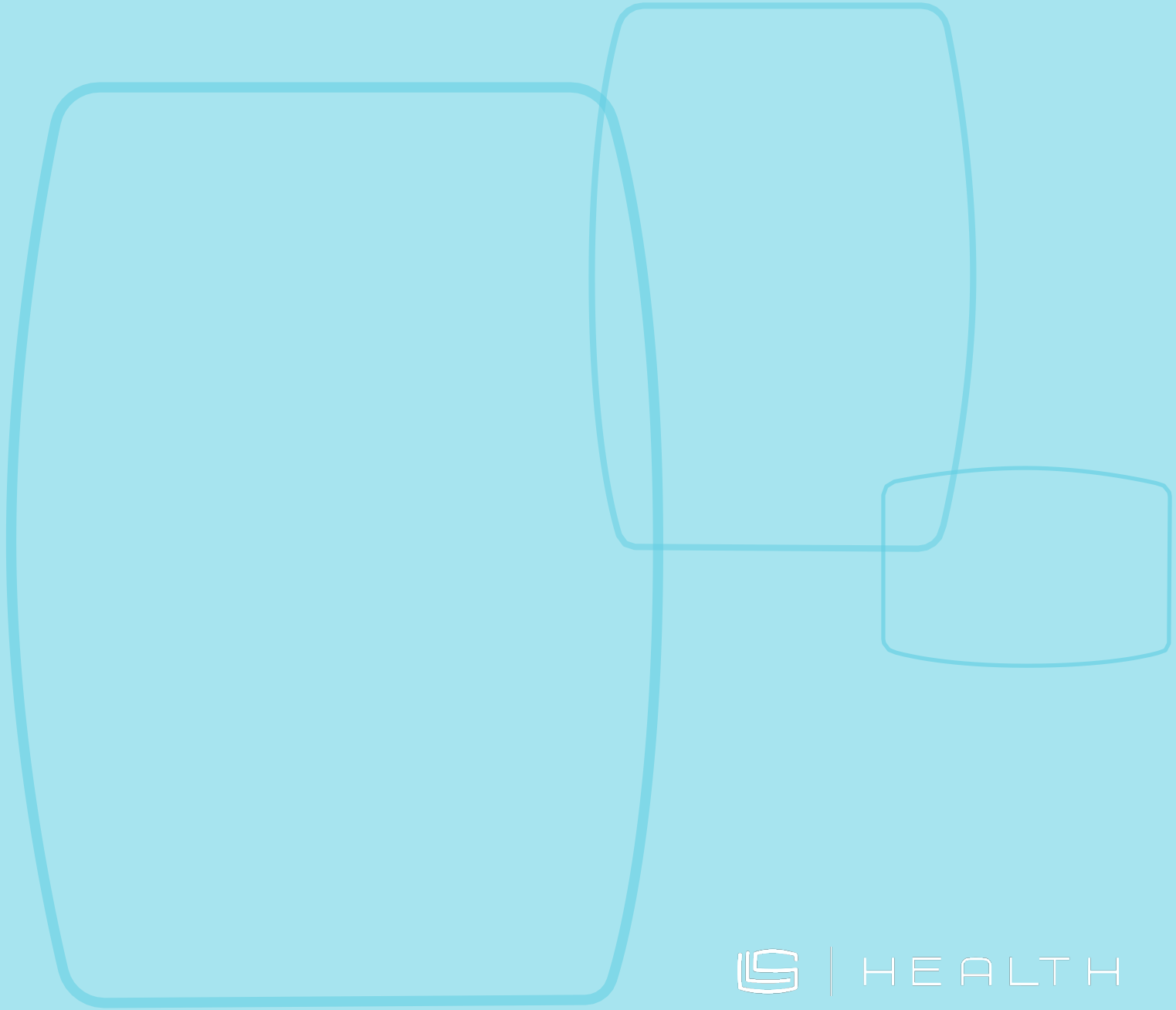

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