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A Solution to Long-Acting Injectable Formulation and Scale-Up Challenges

Microsphere Summit
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October 15, 2025

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Overview

- Oakwood's emulsion/extraction method of continuous microsphere manufacturing
- Formulation parameters
- Process parameters
- Formulation Examples
  - Hydrophobic small molecule
    - In vitro release; SEM analysis
  - Inter-species PK study
- Oakwood's approach to scale-up and evaluation of:
  - Solvent exposure studies (Examples 1-3)
  - Terminal sterilization
- Oakwood Labs company overview

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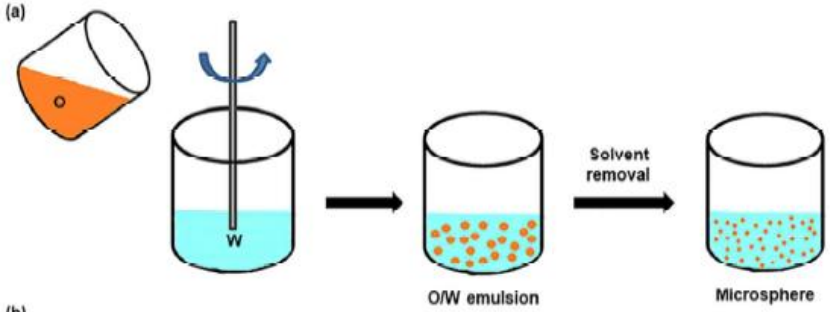
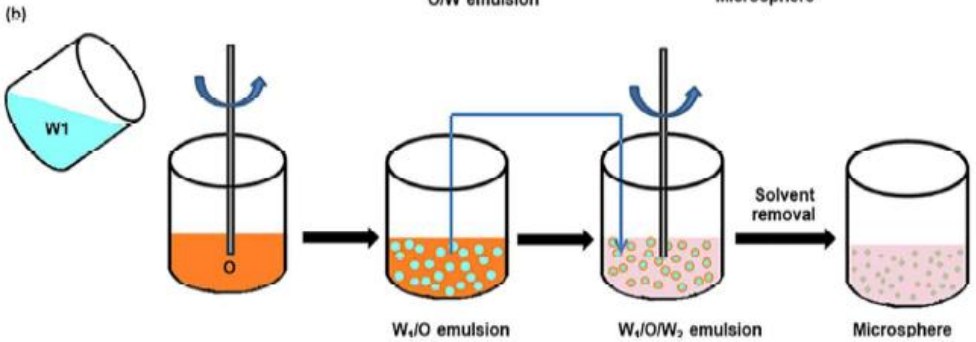
Emulsification/Extraction Homogenization Method

- Emulsion droplets/microspheres formed via fluid shear forces
- Simple equipment, low cost
- Limitations include large size distribution, presence of fines, high shear forces

- Single Emulsion



- Double Emulsion



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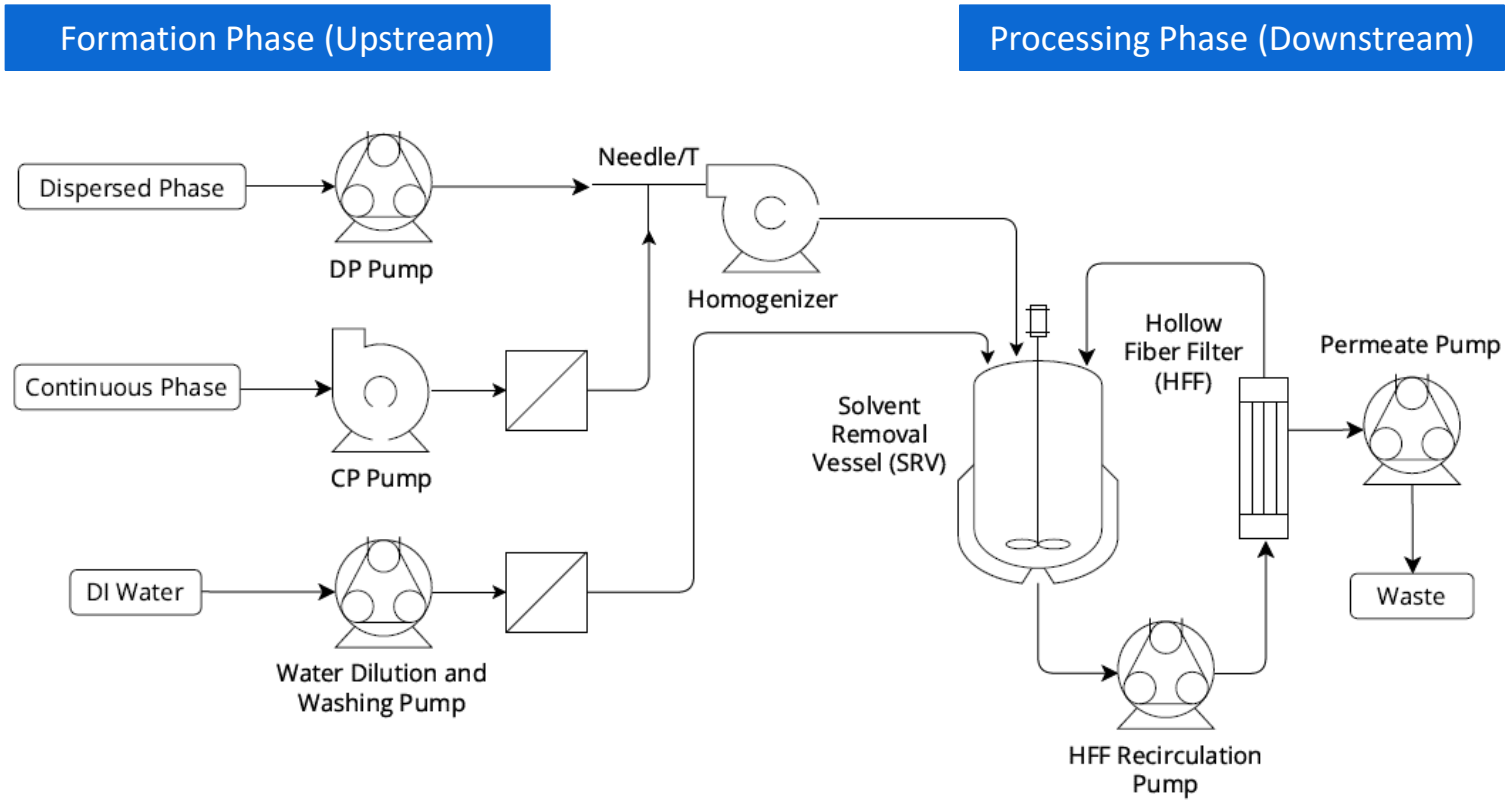
Oakwood Labs' Chronijects™ is an Emulsification/Extraction Two-Phase Process



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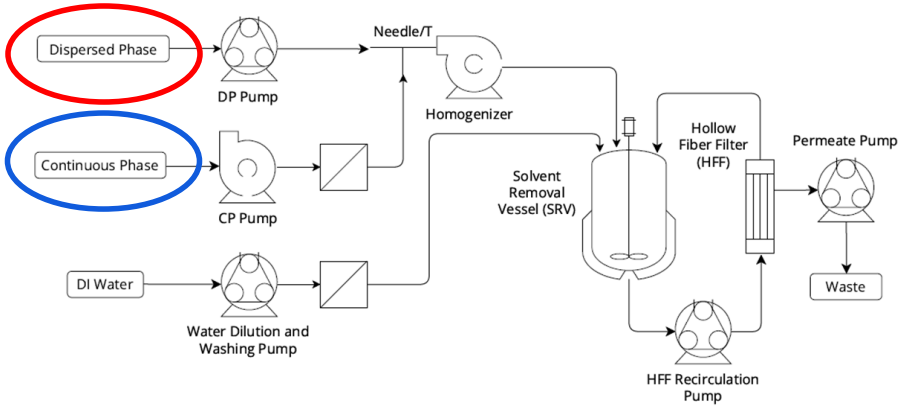
Formulation Parameters

- Dispersed Phase
  - Drug characteristics
    - Solubility
    - Base vs salt
    - Interactions with polymer
  - Target drug load
  - Polymer (co-monomer ratio, MW, end group)
  - Solid content in dispersed phase (i.e. viscosity)
  - Solvent system
- Continuous Phase
  - Surfactant
  - pH
  - Salt



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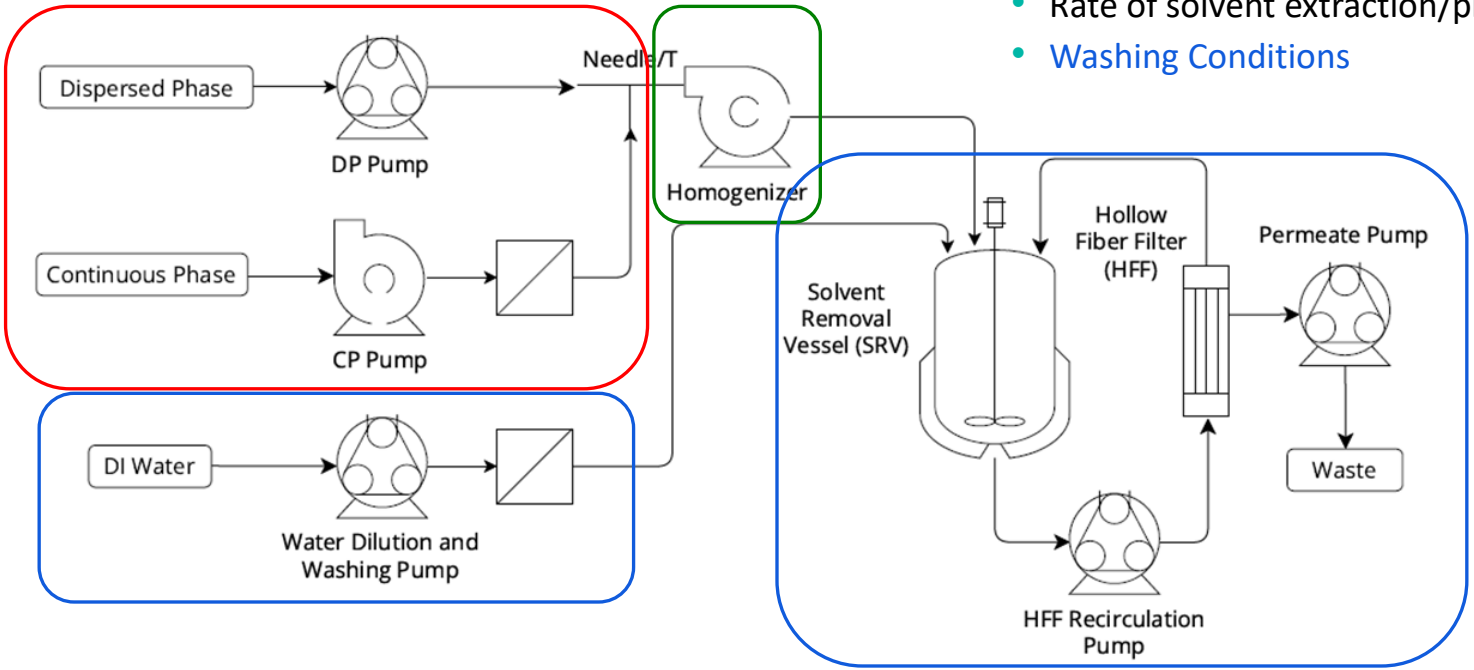
Process Parameters

- Continuous Phase/Dispersed Phase Ratio
- Fluid shear levels within homogenizer
- Homogenizer speed
- Rate of solvent extraction/precipitation
- Washing Conditions



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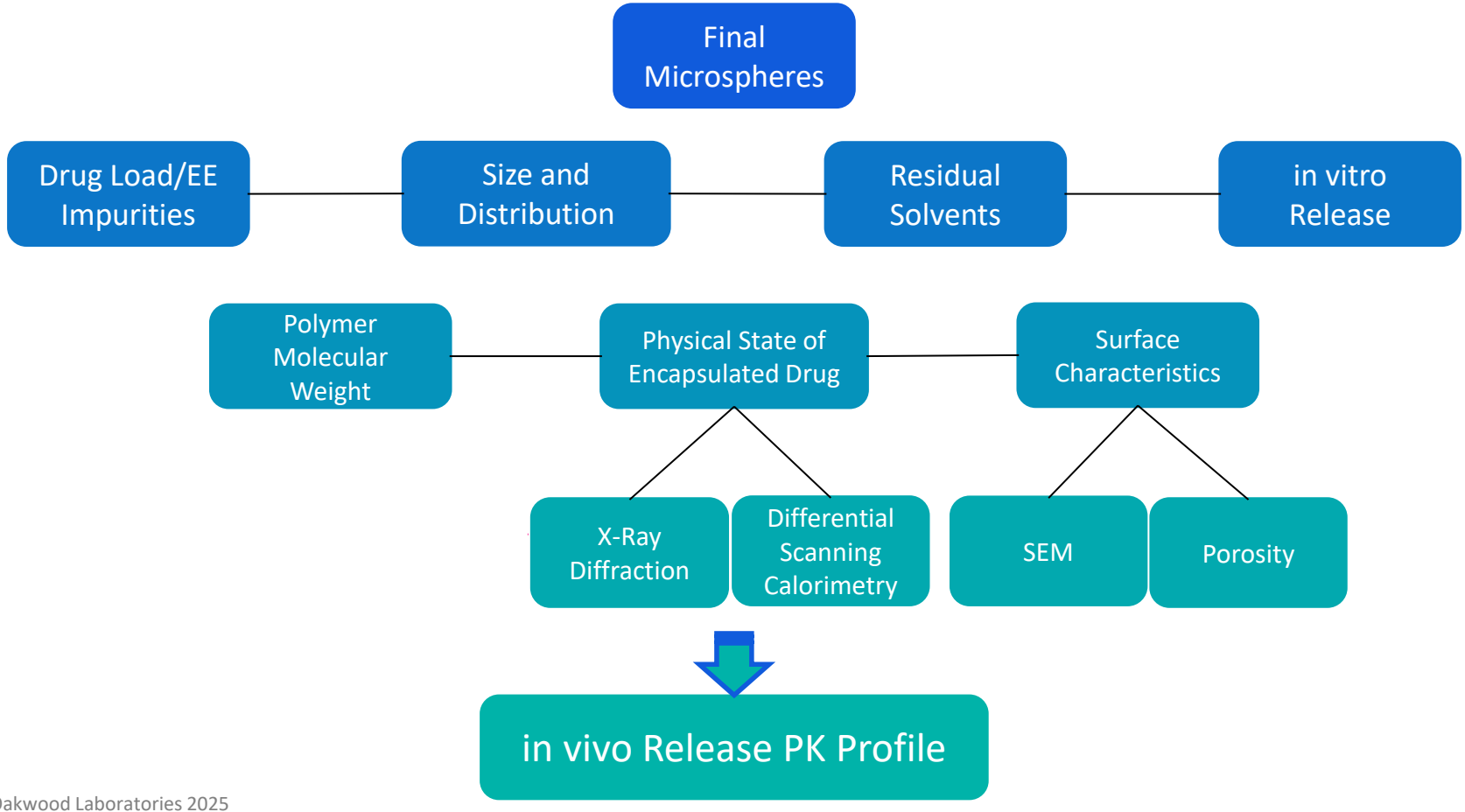
Microsphere Characterization



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Example 1: Hydrophobic Small Molecule

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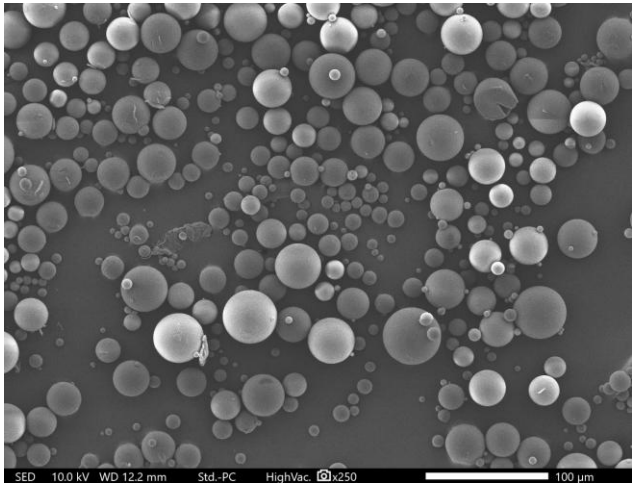
Example 1: Small Molecule (Hydrophobic) Feasibility

- Small scale microsphere batches encapsulating macitentan were manufactured to demonstrate the effects of:
  - Varying polymer
    - Co-monomer ratio
    - Inherent viscosity
  - Varying microsphere
    - Drug load
    - Particle size

Drug Profile:	
Molecule	Macitentan
Molecular Weight (Da)	588.3
Water Solubility	insoluble



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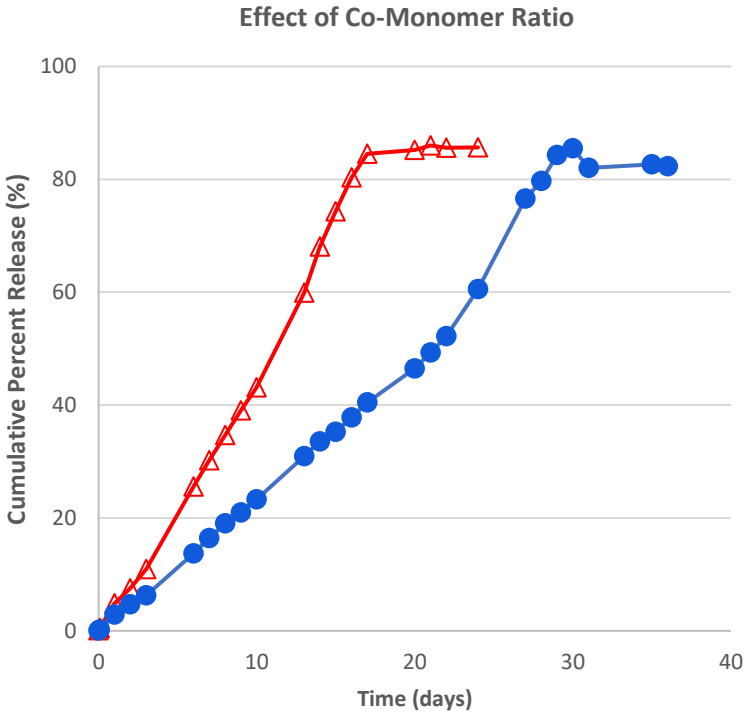
Example 1: Varying Polymer Co-Monomer Ratio

Lot Number	2	4
Symbol	△	●
Polymer [Viatel™]	DLG 7502 A	DLG 8502 A
Co-Monomer Ratio (LA:GA)	75:25	85:15
Polymer End Group	Acid	
Polymer IV (dL/g)	0.22	0.23

*all other microsphere parameters held constant



- Increasing lactide content increases release duration

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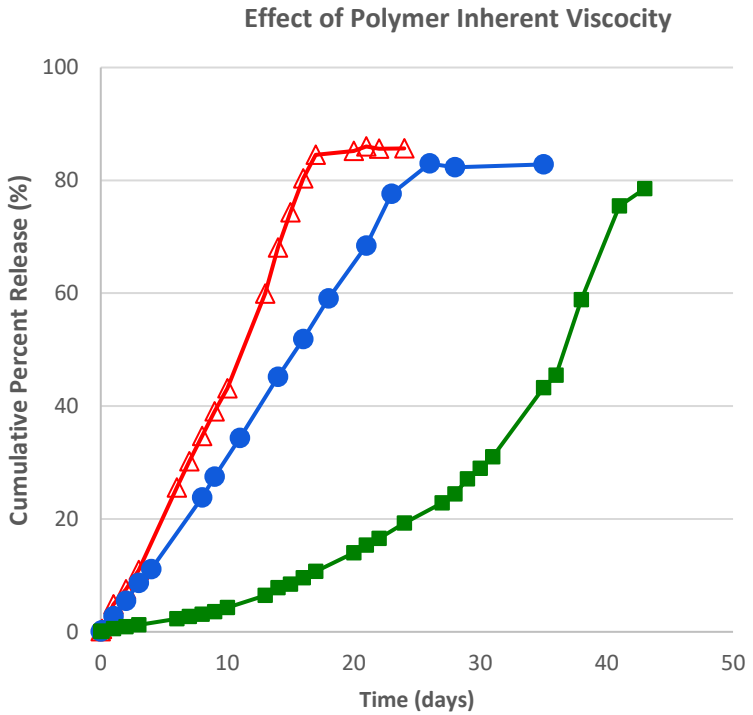
Example 1: Varying Polymer Inherent Viscosity

Lot Number	2	13	3
Symbol	△	●	■
Polymer [Viatel™]	DLG 7502 A	DLG 7503 A	DLG 7503 A
Co-Monomer Ratio (LA:GA)	75:25		
Polymer IV (dL/g)	0.22	0.3	0.39

*all other microsphere parameters held constant

- Increasing polymer inherent viscosity increases release duration



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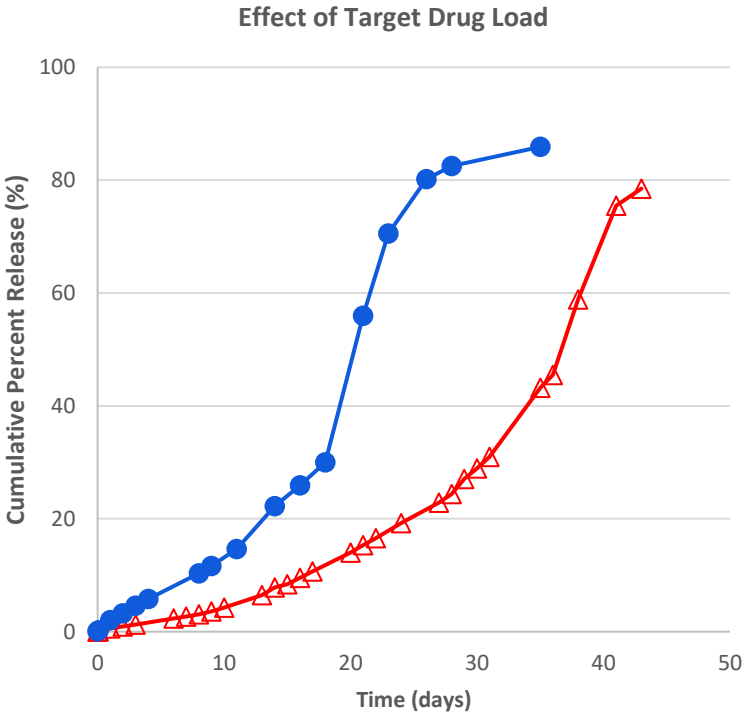
Example 1: Varying Target Drug Load

Lot Number	3	14
Symbol	△	●
Polymer [Viatel™]	DLG 7502 A	
Co-Monomer Ratio (LA:GA)	75:25	
Polymer IV (dL/g)	0.39	
Target Drug Load (wt%)	50	65

*all other microsphere parameters held constant



- Increasing target drug load decreases release duration
  - Less polymer to control release
  - Smaller size due to viscosity changes

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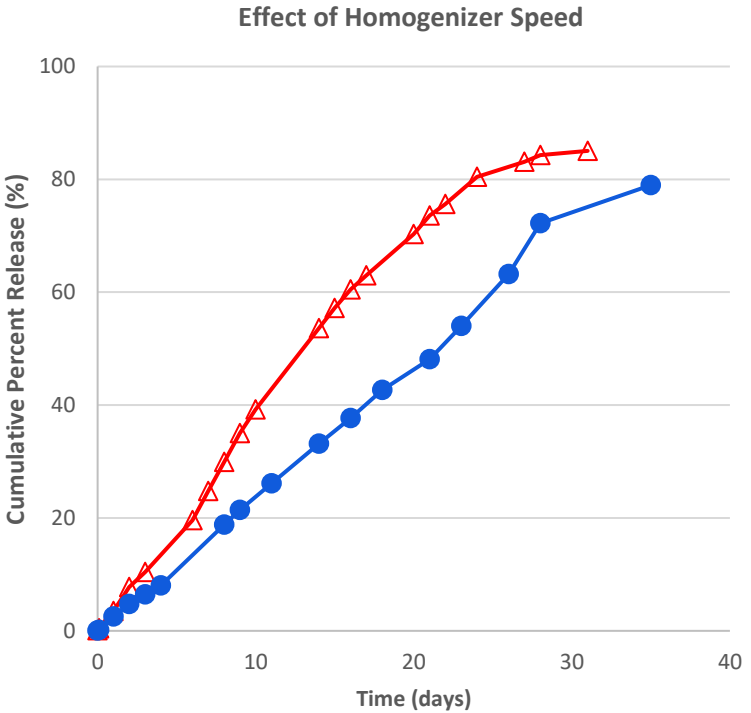
Example 1: Varying Homogenizer Speed/Microsphere Size

Lot Number	15	10
Symbol	△	●
Polymer [Viatel™]	DLG 8502 A	
Co-Monomer Ratio (LA:GA)	85:15	
Polymer IV (dL/g)	0.23	
Homogenizer Speed (rpm)	3500	2250
Average Size (µm)	34	52
Residual DCM (wt%)	0.1	0.7

*all other microsphere parameters held constant



- Increasing homogenizer speed:
  - Decreases microsphere size
  - Decreases residual solvents

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IVR Degradation SEM Images

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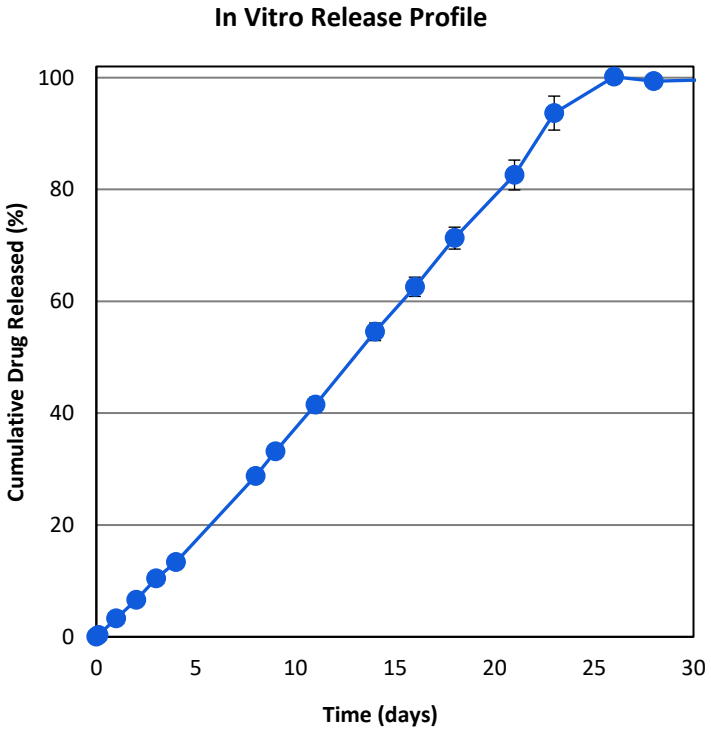
Example 1: IVR Degradation

Polymer, PLGA	75:25
Polymer IV (dL/g)	0.3
Polymer Endcap	Acid
Batch Size (g)	5
Drug Load (%)	50.6
Particle Size, Dv50 (µm)	39



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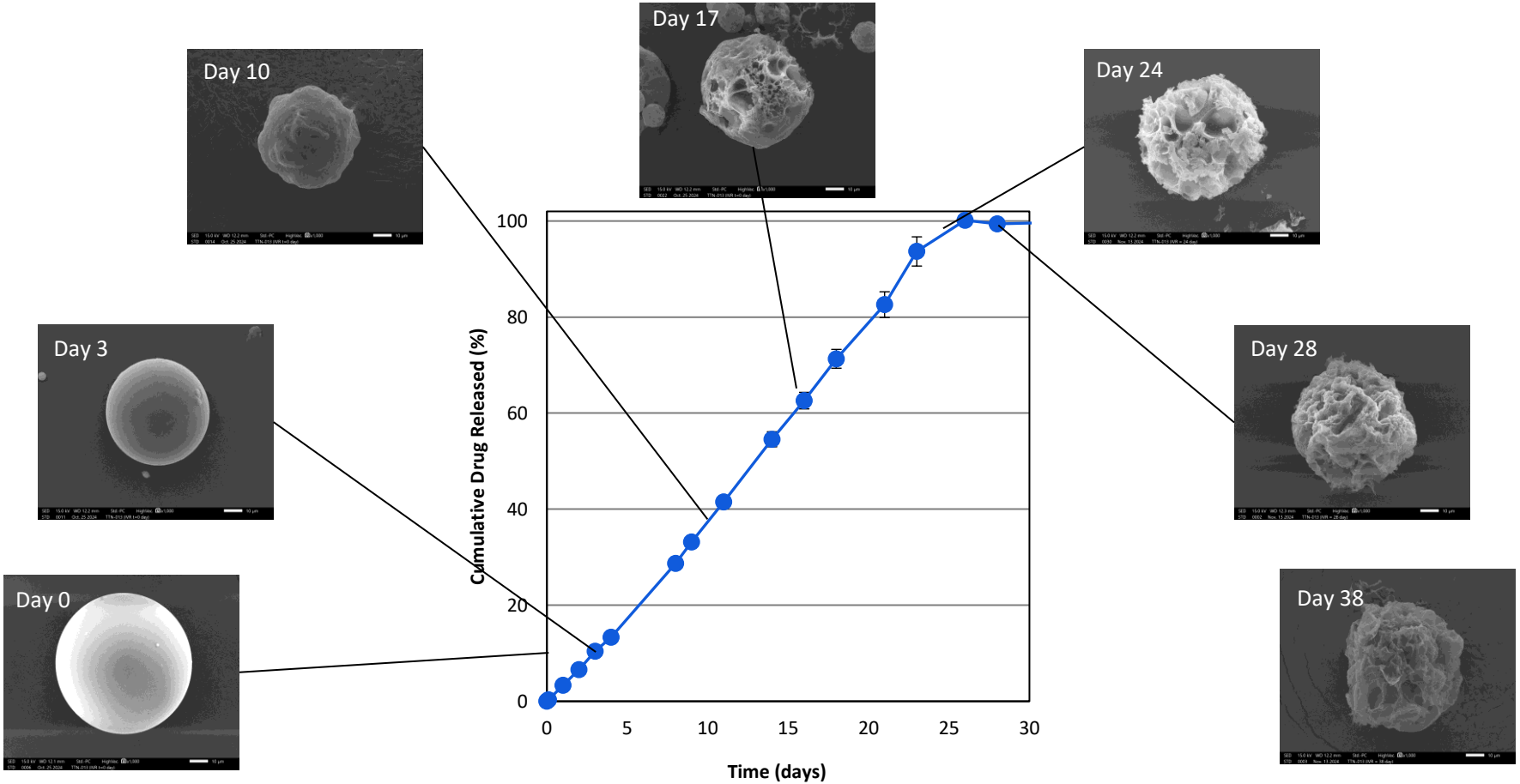
Example 1: SEM of Microsphere Samples Throughout a Release Test



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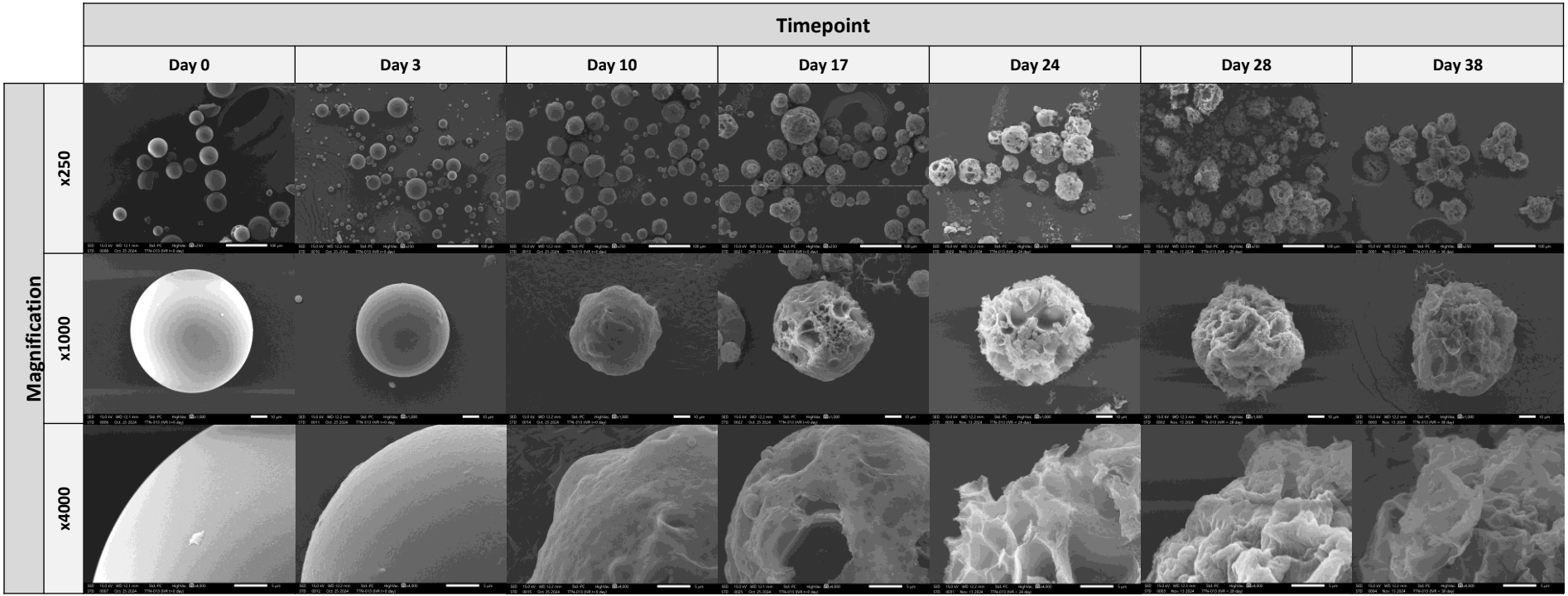
Example 1: IVR Degradation SEM Compilation



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Example 2: Inter-species PK Study

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Example 2: Inter-species PK study

- Small scale microsphere batches encapsulating selexipag were manufactured to demonstrate the effects of:
  - Varying polymer
    - Co-Monomer Ratio
    - Inherent viscosity
  - Varying microsphere
    - Drug load
    - Size
  - PK Study in Rats and Dogs

Drug Profile:	
Molecule	Selexipag
Molecular Weight (Da)	496.6
Water Solubility	Insoluble at low pH
Purpose	Pulmonary arterial hypertension

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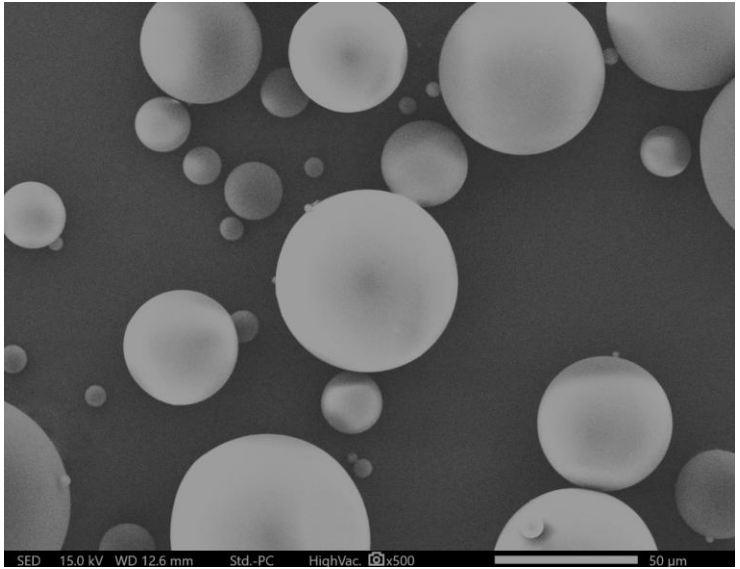
Example 2: Poor in vitro-in vivo Correlation

Lot Number	15
Polymer [Viatel™]	DL 03 A
Co-Monomer Ratio (LA:GA)	100:0
Polymer End Group	Acid
Polymer IV (dL/g)	0.33
Drug Load (wt%)	35.7



- Chosen formulation for animal PK studies

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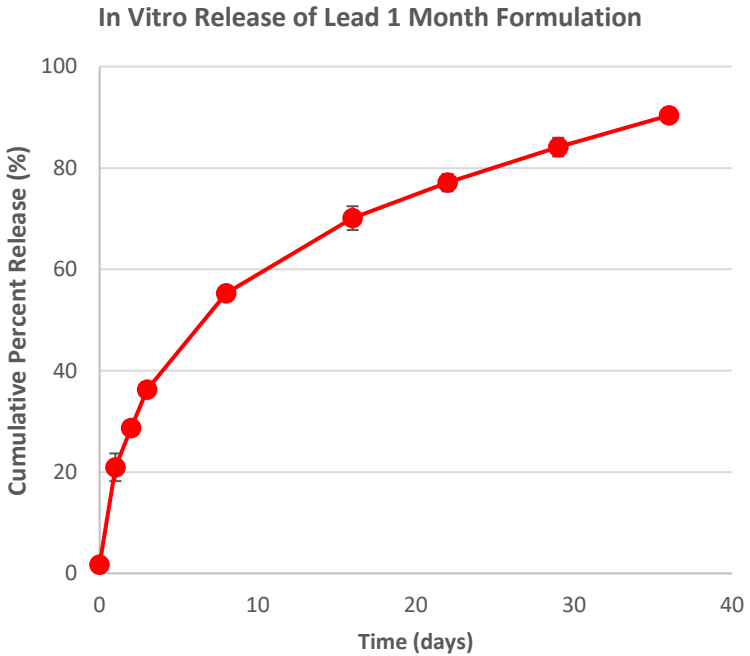
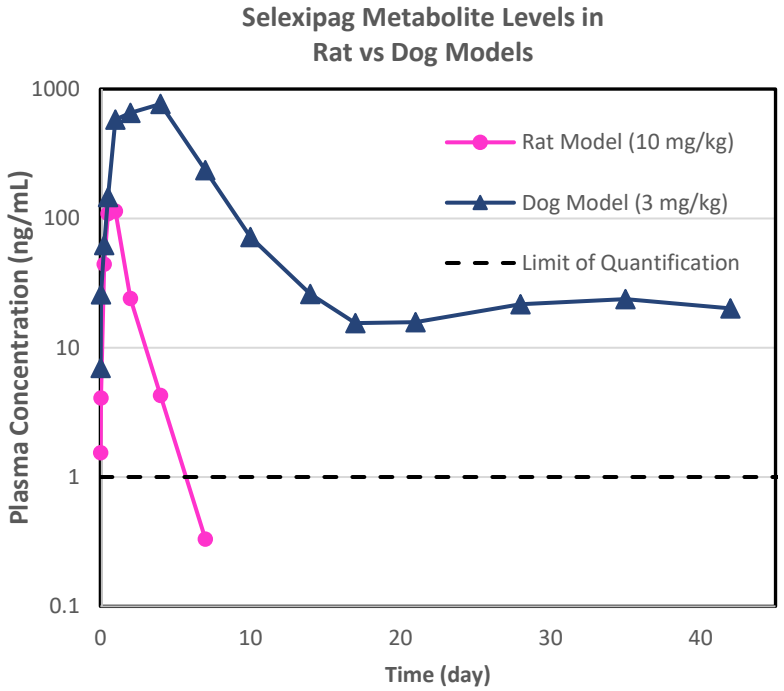
Example 2: Poor in vitro-in vivo Correlation





- Major differences (shape and duration) in PK profiles in rats vs dogs
- Poor in vitro-in vivo correlations

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Scale-Up of Microsphere Formulations

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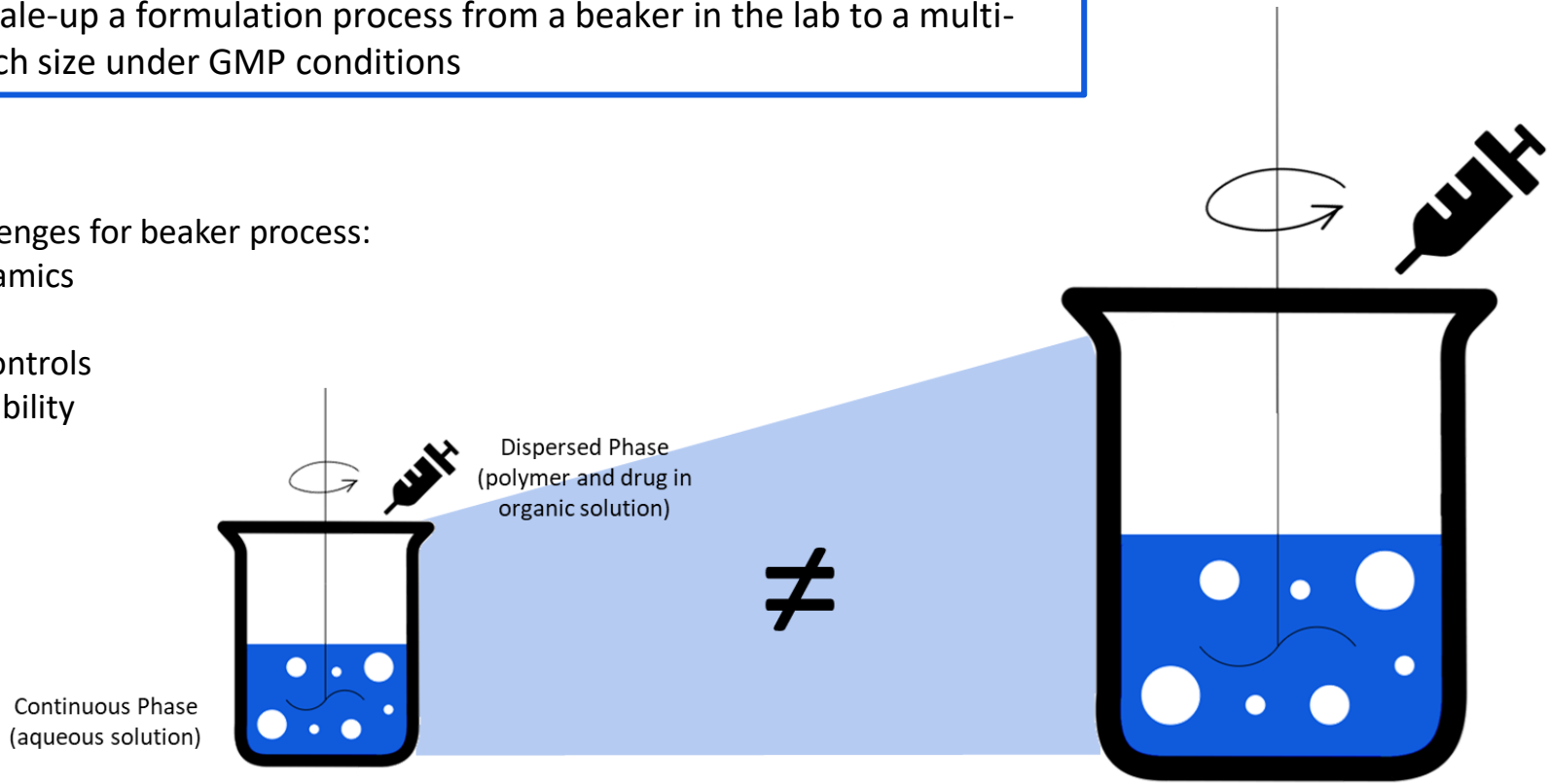
Typical Microsphere Scale-Up Problems

Challenge: scale-up a formulation process from a beaker in the lab to a multi-kilogram batch size under GMP conditions

Scale-up challenges for beaker process:

- Fluid Dynamics
- Sterility
- Process controls
- Reproducibility



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Microsphere Formulation Development: Scale Up Approach

Different Ways to Scale Up:	Pros:	Cons:
Extend the manufacturing time	• No changes to the manufacturing approach • No new equipment required	• Time often has a negative impact on final product, usually due to long duration of solvent exposure on the microspheres • Batch times take significantly longer
Increase the manufacturing rate	• Faster process • Minimizes negative effects of time and solvent exposure	• Requires new equipment train and manufacturing process • Must translate small scale results to larger equipment

The answer is usually a balance of the two approaches; to make material over a longer period of time, and at faster flow rates than the small scale

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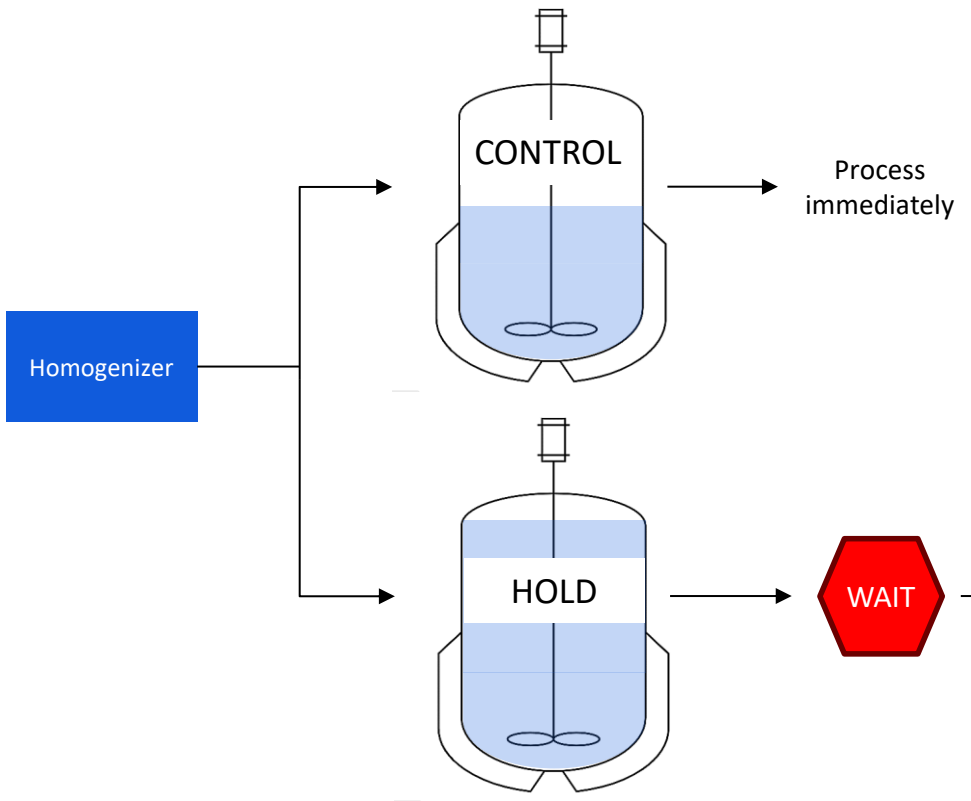
Microsphere Formulation Development: Solvent Exposure Studies



- Small scale solution to large scale testing:
  - Microsphere formulations held in solvent-rich environment to determine effects
  - Designed to mimic longer manufacture times for large-scale formulations (clinical- or commercial-scale), but using a small-scale batch
  - Process half of the batch as normal for small-scale as a control
  - Hold half of the batch for large-scale manufacturing time before processing
- Benefits:
  - Limited material amounts required
  - Potential scale-up challenges identified early on

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Scale-Up: Overcoming Solvent Exposure Effects

- Many formulations will see a negative impact from an increased solvent exposure time/ increased manufacturing time

- Some parameters that can be changed to overcome these negative impacts include:
  - CP:DP ratio
  - Water dilution
  - Manufacturing temperature
  - Solvent system
  - CP composition

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Scale-Up: Example 1 (small molecule)

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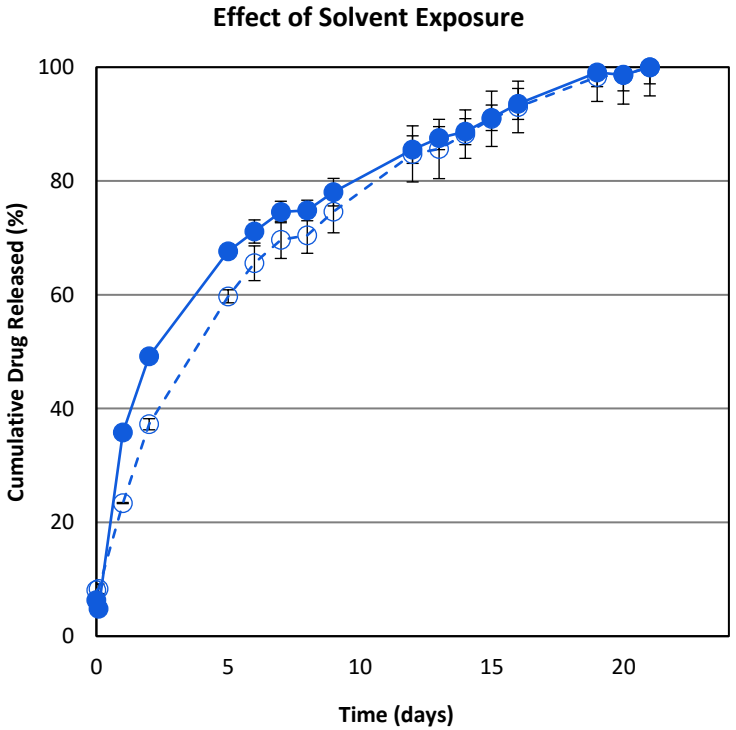
Scale-Up Example 1: Effect of Solvent Exposure

Lot Number	24	
Hold Time (hours)	0	4
Symbol	-●-	···○···
Target Drug Load (%)	50	
Drug Load (%)	49.3	47.3



- Increased solvent exposure duration led to minimal formulation changes with both drug loading and in vitro release profile
  - No formulation changes were necessary to continue development process

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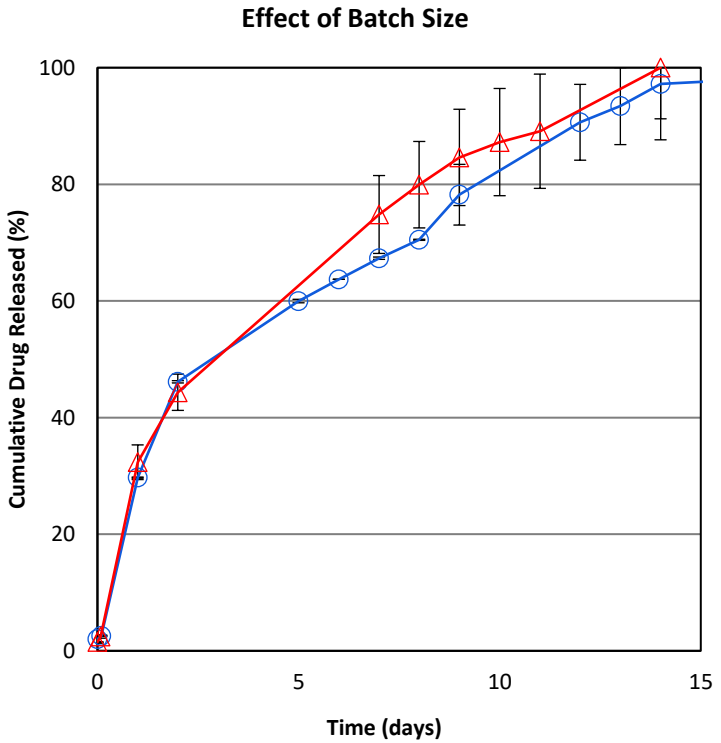
Scale-Up Example 1: Effect of Batch Size

Lot Number	25	26
Symbol	○	△
Batch Size (g)	5	500
Drug Load (%)	49.8	50.2
Avg. Particle Size (µm)	36	39

*all other microsphere parameters held constant

- Increasing batch size (100X) has little to no effect on drug loading and release profile



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Scale-Up: Example 2 (peptide)

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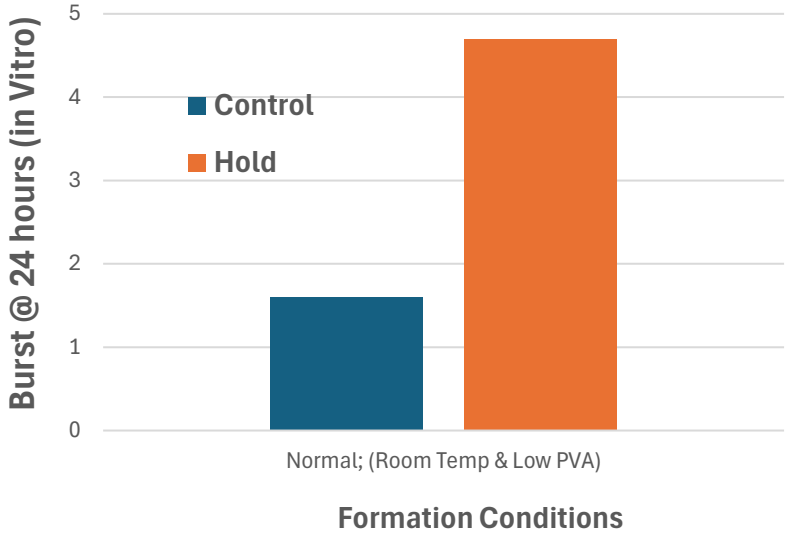
Scale-Up Example 2: Effect of Solvent Exposure

Lot Number	101/102	
Hold Time (hours)	0	4
Target Drug Load (%)	14	
Drug Load (%)	11.4	11.7

- Increased solvent exposure duration led to increase in the burst release, but with no effect on the drug loading
  - Process changes were necessary to continue scale-up development



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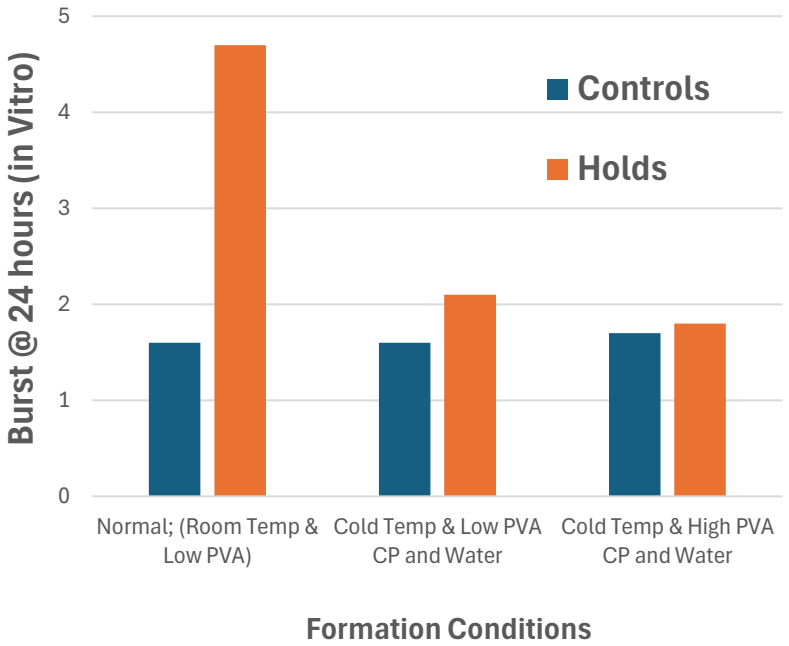
Scale-Up Example 2: Mitigation of Solvent Effect

Lot Number	101/102		111/112		113/114	
	Room Temp CP and Water		Cold CP and Water		Cold CP and Water; High PVA	
Hold Time (hr)	none	4	none	4	none	4
Target Drug Load (%)	14					
Drug Load (%)	11.4	11.7	13.0	12.9	11.3	10.6



- Decreasing the processing temperature minimized the solvent/time effect on the in vitro burst
- However, cold temperatures caused processing changes
- Increasing the PVA concentration in the CP improved processing at the colder temperatures

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Scale-Up: Example 3 (small molecule)

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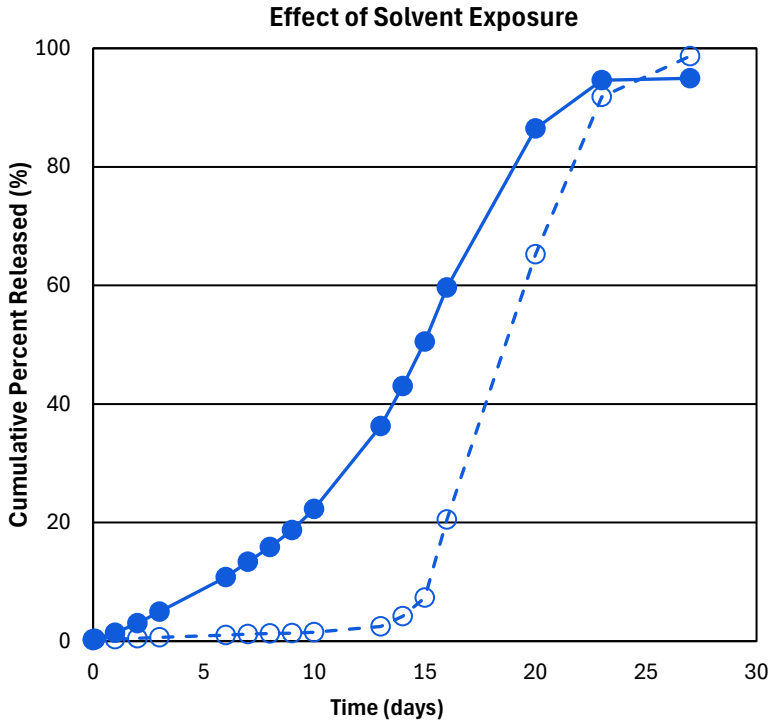
Scale-Up Example 3: Effect of Solvent Exposure

Lot Number	127/128	
Hold Time (hr)	0	4
Symbol	-●-	···○···
Target Drug Load (%)	55	
Drug Load (%)	50.3	45.4

- Increased solvent exposure duration led to lower drug load
- Solvent exposure also produced a lag period
- Process changes were necessary to continue scale-up development



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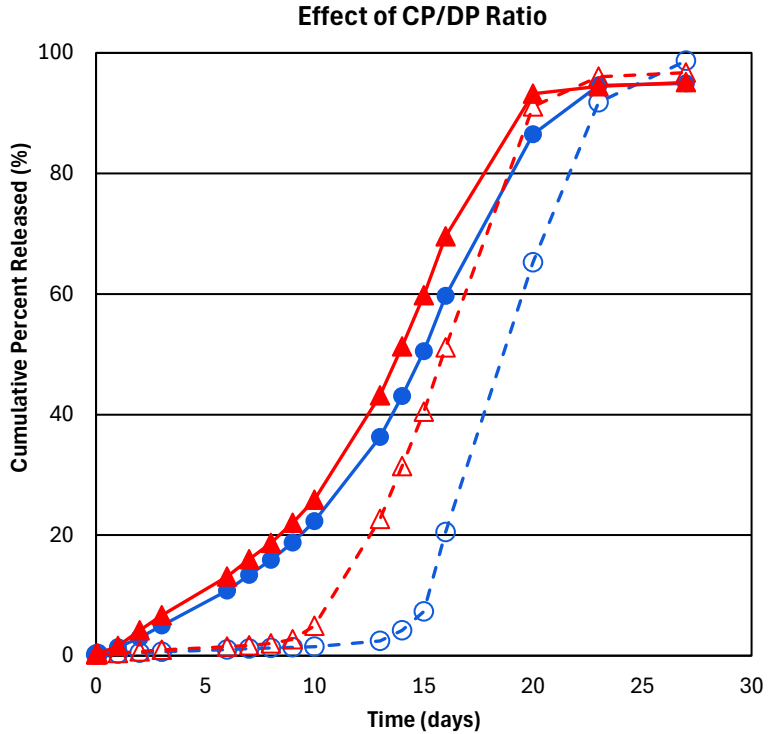
Scale-Up Example 3: Effect of Solvent Exposure

Lot Number	127/128		129/130	
	Room Temp CP and Water		Increased CP/DP Ratio	
Batch Size (g)	20		20	
Hold Time (hr)	none	4	none	4
Symbol	-●-	···○···	-▲-	···△···
Target Drug Load (%)	55			
Drug Load (%)	50.3	45.4	50.5	49.2
CP/DP Ratio	80		120	



- Increasing the CP/DP ratio minimized drug loss during solvent exposure
- However, the IVR lag was still present

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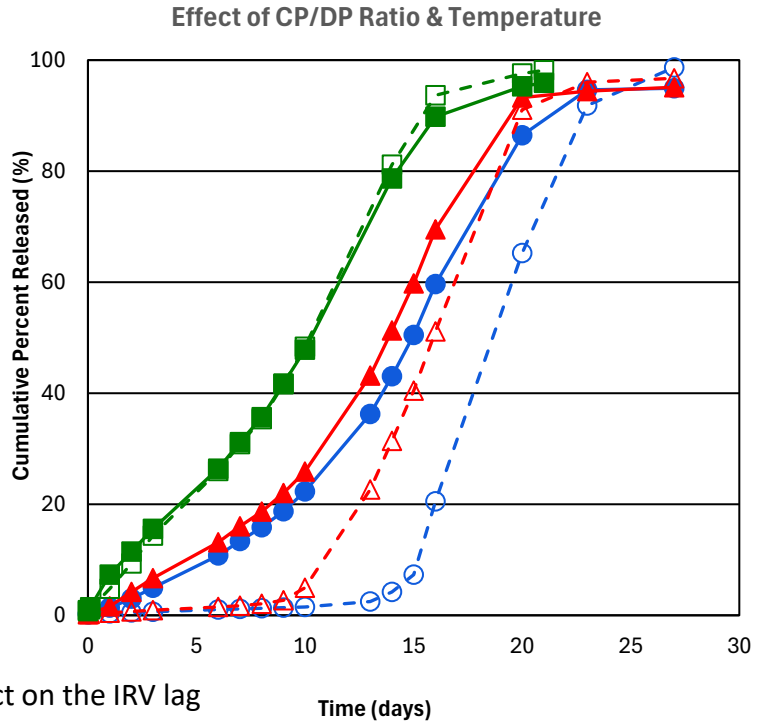
Scale-Up Example 3: Effect of Solvent Exposure

Lot Number	127/128		129/130		136/137	
	Room Temp CP and Water		Increased CP/DP Ratio		Increased CP/DP Ratio Cold CP and Water	
Batch Size (g)	20		20		15	
Hold Time (hr)	none	4	none	4	none	4
Symbol	-●-	···○···	- ▲ -	··· △ ···	-■-	···□···
Target Drug Load (%)	55					
Drug Load (%)	50.3	45.4	50.5	49.2	51.5	51.4
CP/DP Ratio	80		120		120	
Size, D50 (µm)	36	34	38	37	29	28



- Decreasing the processing temperature minimized the solvent/time effect on the IRV lag
- However, smaller particles due to colder temperature; thus, faster release
- Can adjust homogenizer speed to increase microsphere size and thus achieve target IVR profile

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Terminal Sterilization

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Terminal Sterilization Studies

- FDA requires terminal sterilization of injectable drug products, if the product allows
  - Certain APIs degrade during sterilization and therefore require a full aseptic process during manufacturing

- Final product sterilization options include:
  - Irradiation
    - Gamma
    - Electron beam (E-beam)
  - Steam/heat
    - Heat will plasticize polymer in microspheres
  - Factors to consider:
    - Irradiation type
    - Irradiation dose
    - Processing conditions (temperature)

Irradiation Study Conditions		
Irradiation Type	Gamma Irradiation	E-Beam Irradiation
Temperature	Room Temperature (25°C) Frozen (Dry Ice)	Room Temperature (25°C) Frozen (Ice-Packs)
Irradiation Levels	15 kGy 25 kGy 40 kGy	

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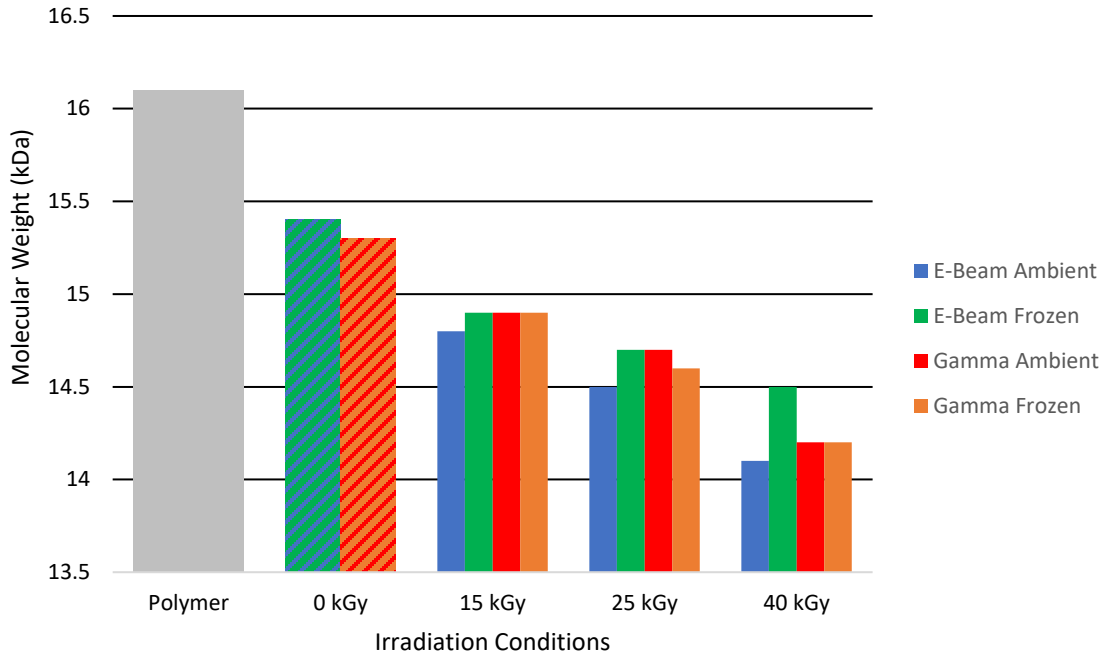
Evaluate Terminal Sterilization: Polymer Molecular Weight Degradation



- Each increase in irradiation dosing resulted in further polymer degradation
- Minimal effect of irradiation type or temperature

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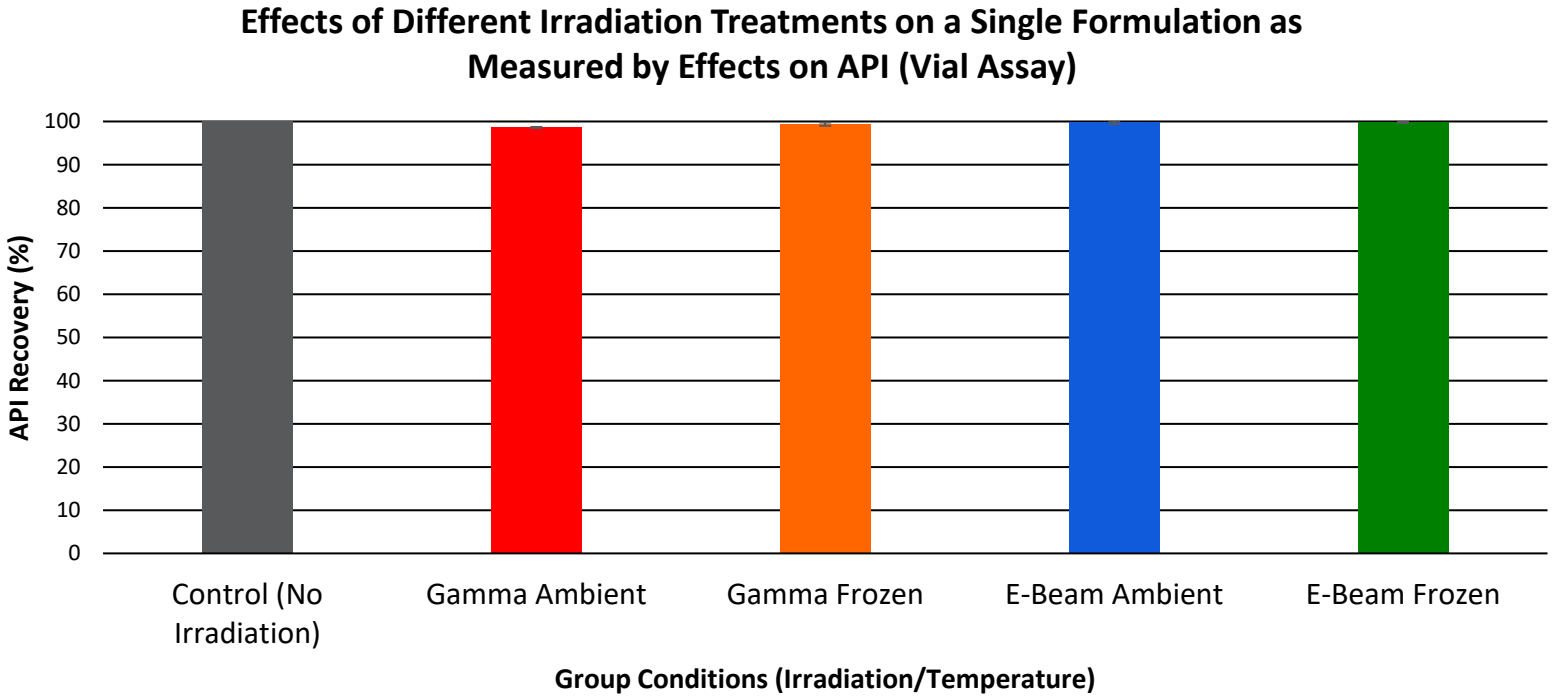
Evaluate Terminal Sterilization: Evaluation of API Degradation



- Minimal effect of irradiation type or temperature on Assay

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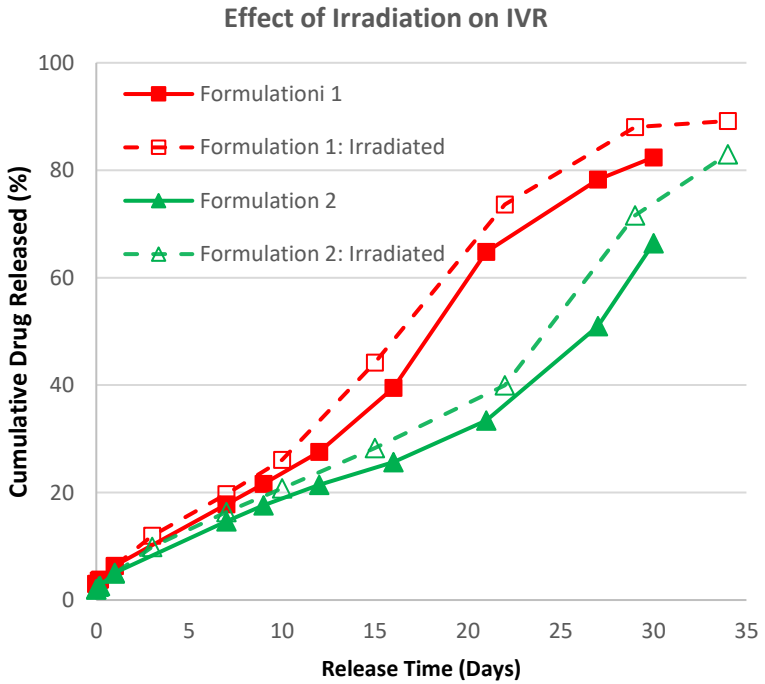
Evaluate Terminal Sterilization: Impact on in vitro Release Duration

Formulation	1	2
Symbol	■	▲
MW Degradation from Irradiation (%)	6.5	9.0



- Irradiation (25 kGy gamma) slightly accelerated *in vitro* release for both formulations

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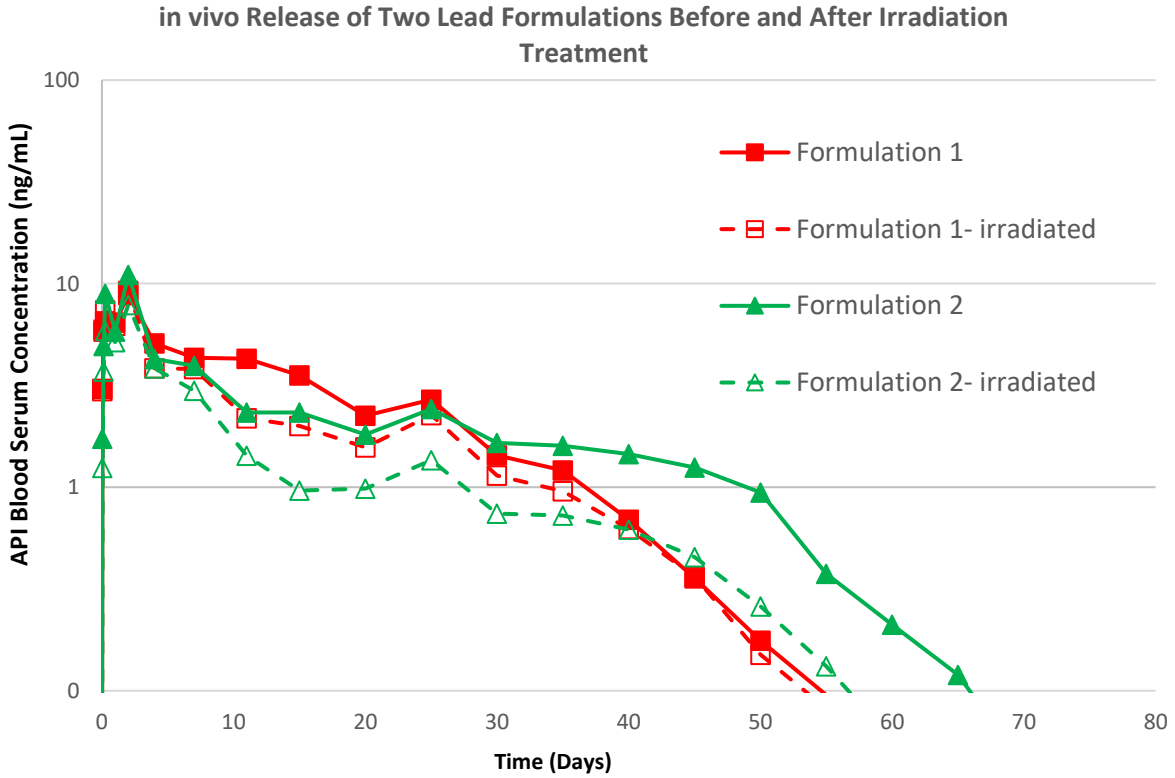
Evaluate Terminal Sterilization: Dog PK Study



- Irradiation (25 kGy gamma) shortened the duration for Formulation 2 only

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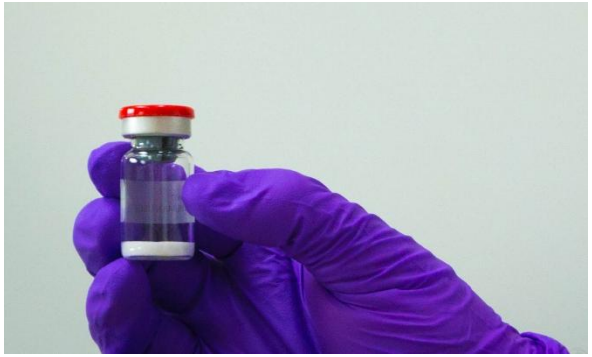
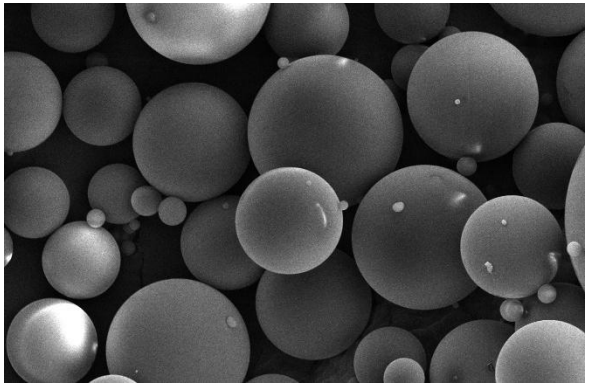
Summary

- During the feasibility stage of microsphere development, many formulation parameters can be tuned to develop the desired product profile
  - Polymer IV
  - Polymer co-monomer ratio
  - Polymer end group
  - Microsphere size
  - Microsphere drug load



- Even with a strong lead formulation from an initial feasibility study, the scale-up process can be challenging, and many factors can influence the success of manufacturing consistent microspheres on any scale



- Oakwood has experience with the unique challenges that each microsphere project presents and can provide a seamless process from feasibility all the way through scale-up and transfer to a GMP facility

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Oakwood Labs

Company Overview

- 75 employees; privately owned
- 28+ years experience as a CDMO partner
- Located in Cleveland, OH, USA
- 1400 m^2 R&D Facility
- 2500 m^2 FDA-approved GMP Aseptic Manufacturing Facility

Research and Development

- Experience with 100+ long-acting injectable programs
- Diverse intellectual property portfolio covering the microsphere manufacturing process
- Microsphere formulations typically using PLA and PLGA polymers
- Analytical capabilities including method development, characterization, and stability

Chroniject™ Technology

- Customizable release durations from 3 days up to 1 year +
- Proven scalability from 3-gram to 30-kilogram batch size
- Ability to encapsulate small molecules, peptides, and proteins
- Applications in multiple therapeutic indications including CNS, Pain, Oncology, Ophthalmology, Animal Health

GMP Manufacturing

- FDA approved cGMP aseptic facility
- In-house QC Chemistry, QC Microbiology, and Quality capabilities
- Successful manufacture and release of multiple phase III global clinical batches
- CMO for sterile injectables manufacturing 5 commercial products

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