Welcome

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New USP General Chapter <1156> LG Polymer Microparticle Drug Products — Characterization Methods

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Agenda

- Background & Scope
- Key Features of LG Microparticles
- Critical Quality Attributes
- Manufacturing Overview
- Characterization Framework
- Imaging & Advanced Techniques
- Quality Tests Summary
- Why Your Input Matters
- Next Steps
- Summary of USP's PLG Excipient Activities

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1 Background

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Background

Stakeholder Engagement

- USP Complex Generics Team engaged with multiple stakeholders globally:
  - Visits to generic companies in India
  - Interactions with companies in the USA and Europe
- Strong demand for:
  - LG Polymer standards
  - USP General Chapter on Microspheres/Microparticles
- Expert Panel formed in **2024** to develop the “LG Polymer Microparticle” chapter
  - Introduces the essential product quality and characterization tests lactide-glycolide (LG) polymer- based microparticle preparations

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Why This Chapter?

- Growing use of Lactide/Glycolide polymer microparticles in long-acting injectables.
- Need for standardized quality tests and characterization methods.

Scope

- Focuses on marketed LG polymer microparticle drug products.
- Excludes implants and non-LG systems.

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Key Features of LG Microparticles

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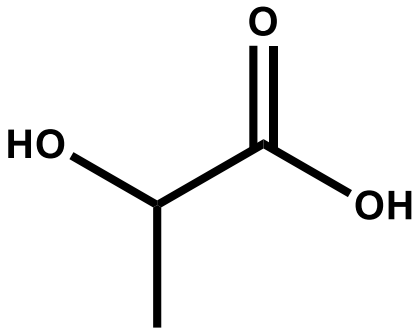
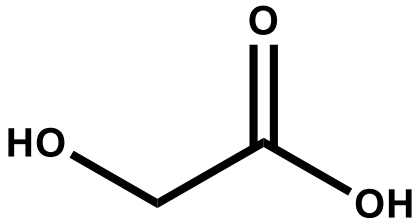
Key Features of LG Microparticles

Polycondensation and Ring-Opening Polymerizations



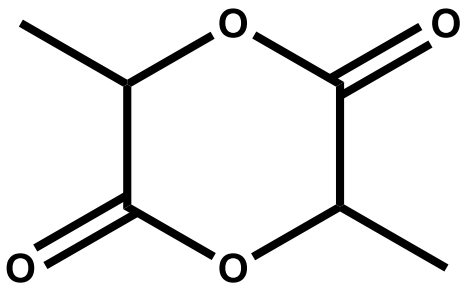
Lactic acid



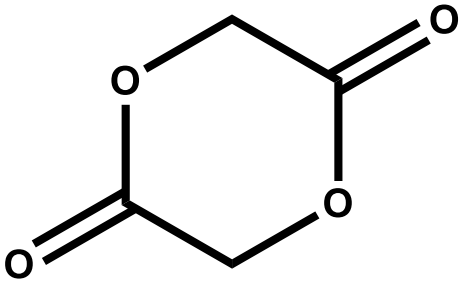
Glycolic acid

Condensation of 2-α–hydroxy acids
(- H_2O)

Poly(lactic acid-co-glycolic acid)
PLGA



Lactide



Glycolide

Ring-Opening Polymerization

Poly(lactide-co-glycolide)
PLG

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Key Features of PLG Microparticles

Poly (lactide-co-glycolide) (PLG) based microparticles are a sustained release drug delivery system (up to 6 months). More than 25 products approved by FDA.

PLG polymers are bioabsorbable, biocompatible and available in several L/G ratios and molecular weights, e.g.,

- (50:50); (65:35); (75:25); (85:15); (90:10); (100:0)

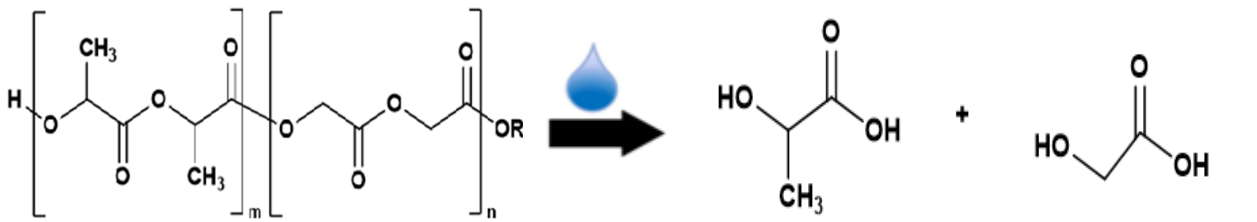
Extended-release of drug over days to months.

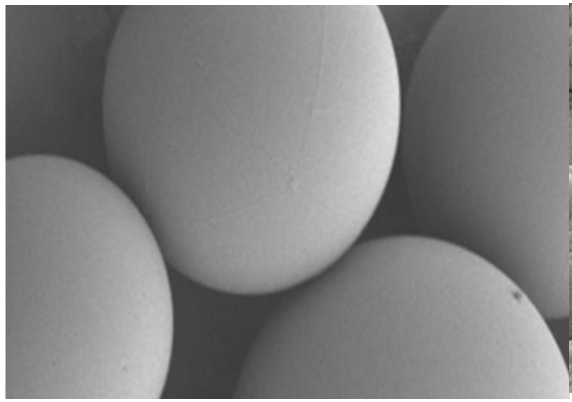
Typical size: 20–50 µm (injectable), up to 300 µm

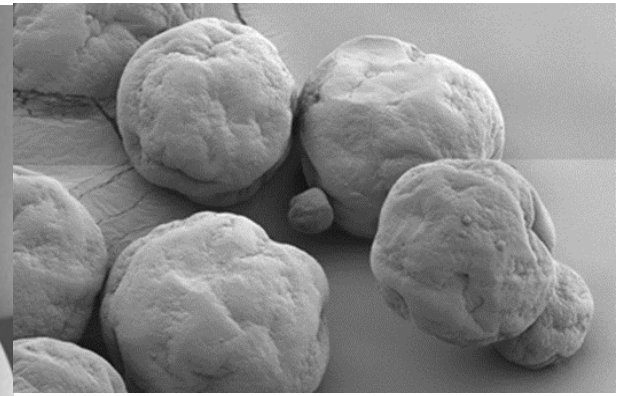
Matrix structure with drug dispersed in polymer.

Supports *Small molécules, peptides, proteins*

- Preferred term is "*Microparticle*"
- Microsphere is not a preferred term because not all drug products are perfectly spherical
- PLG [Poly(lactide-co-glycolide)] polymers







3 Critical Quality Attributes

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PLG qualitative (Q1) and quantitative (Q2) sameness parameters:

- Polymer Synthesis:
  - Direct polycondensation of Lactic acid and Glycolic acid
  - Ring-opening polymerization of the cyclic dimers, Lactide and Glycolide
- Monomer composition: the L:G ratio
  - 50:50 (high rate of degradation), 75:25, 85:15, 90:10 (L:G ratio)
- Terminal group:
  - Acid (faster degradation); Ester (slower degradation)
- Measurement of Molecular Weight:
- GGG Block length
- Polymer chain branching

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Manufacturing Overview

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Manufacturing Overview

- **Microencapsulation Processes**
- **Techniques:**
  - **Emulsion-based** (oil-in-water, double emulsions)
  - **Phase separation** (polymer-polymer incompatibility)
  - **Spray drying**
- **Product by process**
- **Impact on Product**
  - Particle size, morphology, porosity
  - Drug release kinetics
  - Encapsulation efficiency (hydrophobic vs. hydrophilic drugs)
- **Drying Methods**
  - **Air drying, lyophilization**
  - Tg affects microparticle aggregation; storage at **2° to 8°C** recommended
- **Mechanism of Drug Release**
  - **Controlled by Water Influx**
    - Water dissolves drug and hydrolyzes LG polymer
    - Hydrolysis → chain scission → lactic & glycolic acid
    - Polymer swelling enhances drug release
    - Transition to **hydrogel** and eventual **bioabsorption**

Key Factors

  - Drug solubility
  - Polymer hydrophobicity (L:G ratio)
  - Molecular weight
  - Particle size

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5 Characterization Framework

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PLGA qualitative (Q1) and quantitative (Q2) testing methods:

- PLGA synthesis:
  - Block length by ^{13}C NMR (polycondensation vs ring-opening)
  - Block length value – lower value polycondensation, higher value ring-opening
- GA/ LA ratio and Blockiness:
  - Quantitative ^{1}H NMR (qNMR), using the peak areas of LA and GA with an Internal standard
  - ^{13}C NMR for blockiness (shift of glycolide carbonyl) – adjacent to another glycolide or lactide
- Terminal group and number:
  - ^{13}C NMR for the presence of acid groups as well as ester peaks
- Molecular Weight:
  - SEC-RI, SEC-HPLC, SEC-MALS, including 4D (RI, viscometer, static light scattering and dynamic light scattering)
- Polymer chain branching
  - NMR (^{1}H and ^{13}C) Used for branching

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PLG based microparticles CQAs and methods:

- Drug loading:
  - Drug release
  - Inter-batch stability (process maturity)
- Particle size and distribution:
  - Degradation rate
  - Sieving method; Light microscopy (LM); Laser light scattering (LLS)
- Morphology:
  - Shape and surface; cross section – internal microstructure
  - Advanced analytical techniques (next slides)
- Porosity:
  - Pore size and pore distribution
  - Mercury intrusion porosimeter - % Porosity and the average pore diameter

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6 Imaging & Advanced Techniques

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Advanced Techniques

Imaging & Microscopy

- **Light Microscopy, SEM, TEM**
- **MicroCT, FIB-SEM, Raman Imaging**
- Surface & internal morphology
- Porosity, pore size, drug distribution

Quantitative Image Analysis

- Segmentation, resolution vs. representativeness
- Correlative imaging (2D + 3D, structural + chemical)
- Supports **CQA identification and QC strategies**

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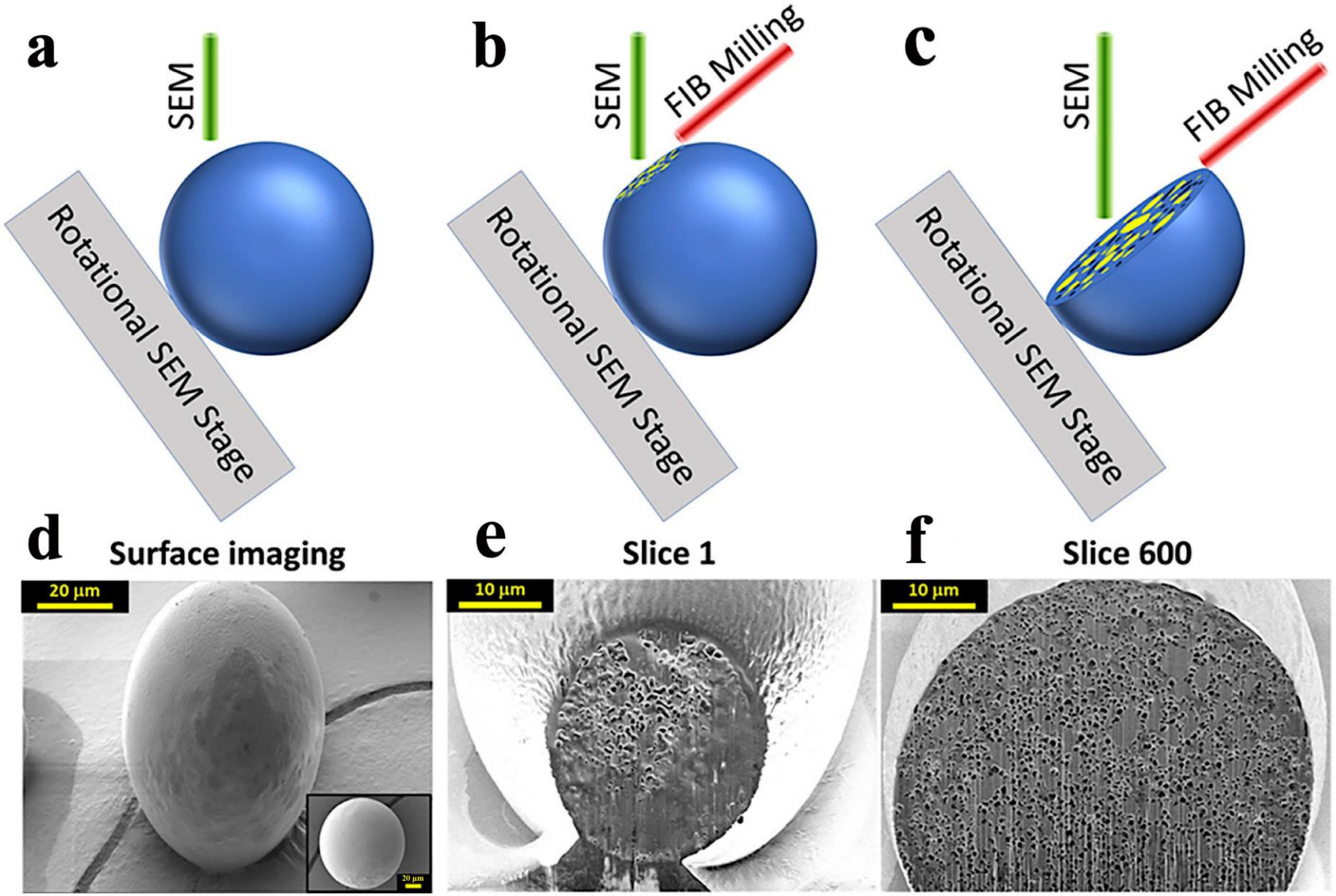
Methods for the Microstructure Characterization (Q3): 1 of 2

Technique	Purpose	Advantages
Focused ion beam scanning electron microscopy (FIB-SEM)	Investigation of PLG, API and porosity distribution of microparticles To mill materials and prepare subsurface cross sections of a sample	• High resolution imaging • 2D imaging and 3D nano-tomographic imaging • Through repeated FIB milling and subsequent SEM imaging, a microparticle structure can be tomographically reconstructed
Energy dispersive spectroscopy (EDX)	Identification of the elements of the material on the microparticle surface	• Identification and quantitation of elemental composition
Synchrotron radiation X-ray microcomputed tomography (SRμCT)	Investigation of the 3D internal structure of microparticles	• 2D and 3D visualization of internal and external geometric structures • High penetration power • High temporal resolution imaging

Methods for the Microstructure Characterization (Q3): 2 of 2

Technique	Purpose	Advantages
X-ray microscopy (XRM)	Characterization of the microstructure of microparticles	• 3D imaging • Non-invasive • High throughput
Confocal Raman microscopy (CRM)	Investigation of the drug distribution and 3D shape of microparticles by Chemical and Spatial analysis of microparticles	• High resolution imaging • Horizontal (x, y) and vertical (x, y and z) imaging
Time-of-flight secondary ion mass spectrometry (TOF-SIMS)	Identification of the chemical composition on the surface of microparticles	• High resolution imaging • 3D image information • High sensitivity and low detection limit

Schematic overview of FIB-SEM imaging of PLG microparticle sample



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7 Quality Tests Summary

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Drug Product Quality Tests

Universal Tests

- Identification, assay, impurities
- Particulate matter ⟨788⟩
- Endotoxins ⟨85⟩, sterility ⟨71⟩
- Residual solvents ⟨467⟩
- Container integrity ⟨1207⟩

Specific Tests

- Particle size ⟨429⟩, ⟨430⟩
- In vitro release ⟨711⟩, ⟨1001⟩
- Resuspendability ⟨1003⟩
- Syringeability
- Water content ⟨921⟩

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Why Your Input Matters

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Stakeholder Inputs

- Industry expertise ensures practical implementation.
- Aligns with current practices and regulatory expectations.
- PF 51(6) publication in Nov 2025.
- Request for comments during public review.
- Feedback shapes final chapter content.

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9 Next Steps

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Next Steps

Next Steps →

- Review PF publication.
- Submit comments via USP contact channels.
- Timeline: PF publication → comment period (90 days) → comments evaluation → finalization or republication after addressing stakeholder comments → Final step (USP-NF Chapter)

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Summary on USP's PLG/PLGA Excipient Activities

Compendial Work

Type	Item #	Publish time	PF	Title	Released or Proposed new USP Reference Standard (RS)	Comments
Stimuli article	1	2022/03	48 (2)	A Practical Approach to Compendial Nomenclature and Testing For Lactide and Glycolide Polymers and Related Polymeric Excipients	NA	
	2	2023/11	49 (6)	USP Responses to Comments on Stimuli Article: "A Practical Approach to Compendial Nomenclature and Testing for Lactide and Glycolide Polymers and Related Polymeric Excipients"	NA	
Monograph	1	2022/05	48 (3)	DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid	USP DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid RS	**Became official in USP-NF 2025 Issue 1 in May 2025; The RSs have been released.**
	2	2022/11	48 (6)	DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester	USP DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester RS	
	3	2023/09	49 (5)	DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid	USP DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid RS	
	4	2024/07	50 (4)	DL-Lactide Homopolymer 14000 Acid	USP DL-Lactide Homopolymer 14000 Acid RS	Will become official in USP-NF 2026 Issue 2 in April 2026
	5	2025/07	51 (4)	DL-Lactide and Glycolide (50:50) Copolymer 63000 Acid	USP DL-Lactide and Glycolide (50:50) Copolymer 63000 Acid RS	In pipeline
	6	2025/07	51 (4)	DL-Lactide and Glycolide (75:25) Copolymer 20000 Acid	USP DL-Lactide and Glycolide (75:25) Copolymer 20000 Acid RS	In pipeline
	7	2026/07 (target)	52 (4) (target)	DL-Lactide and Glycolide (85:15) Copolymer 23000 Hexanediyl Ester	USP DL-Lactide and Glycolide (85:15) Copolymer 23000 Hexanediyl Ester RS	UNII#93PPD1S477
	8	TBD	TBD	DL-Lactide Homopolymer XXX Acid (TBD)	To be proposed	In pipeline; for POLYLACTIDE with UNII #459TN2L5F5 in FDA IID.
General chapter (GC)	1	2024/09	50 (5)	<315> NMR Spectroscopy Number-average Molecular Weight Determination for Lactide or Lactic Acid and Glycolide or Glycolic Acid Polymers.	NA	Prospectus: https://www.uspnf.com/notices/gc-315-prospectus-20231229; Will become official in USP-NF 2026 Issue 2 in April 2026
	2	2024/09	50 (5)	<316> Gel Permeation Chromatography Molecular Weight and Polydispersity determination for Lactide or Lactic Acid and Glycolide or Glycolic Acid Polymers using Universal Calibration.	NA	Prospectus: https://www.uspnf.com/notices/gc-316-prospectus-20231229; Will become official in USP-NF 2026 Issue 2 in April 2026
	3	2025/07	51 (4)	<318> Nuclear Magnetic Resonance Spectroscopy Monomer Ratio Determination for Lactide-Glycolide Polymers	NA	Prospectus: https://www.uspnf.com/notices/318-gc-prospectus-20241025
	4	2026/03 (target)	52 (2) (target)	<319> Nuclear Magnetic Resonance Spectroscopy Block Length Determination for Lactide-Glycolide Polymers	NA	In development
	5	TBD	TBD	<324> Size Exclusion Chromatography Molecular Weight and Polydispersity Determination for Lactide-Glycolide Polymers	6 50:50 LG polymer calibrants and 7 75:25 LG polymer calibrants	In development

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Emerging Solution Work

- Analytical Reference Materials (ARMs) and an associated case study
  - USP has been working on developing 19 LG polymer ARMs, with **7** already launched:
    - PLG 50:50 DLLG 4E
    - PLG 50:50 DLLG 5E
    - PLG 75:25 DLLG 3E
    - PLG 75:25 DLLG 5E
    - PLG 75:25 DLLG 7E
    - PLG 75:25 DLLG 9E
    - PLG 75:25 DLLG 10E
  - The case study is available at **USP LG polymer webpage**.

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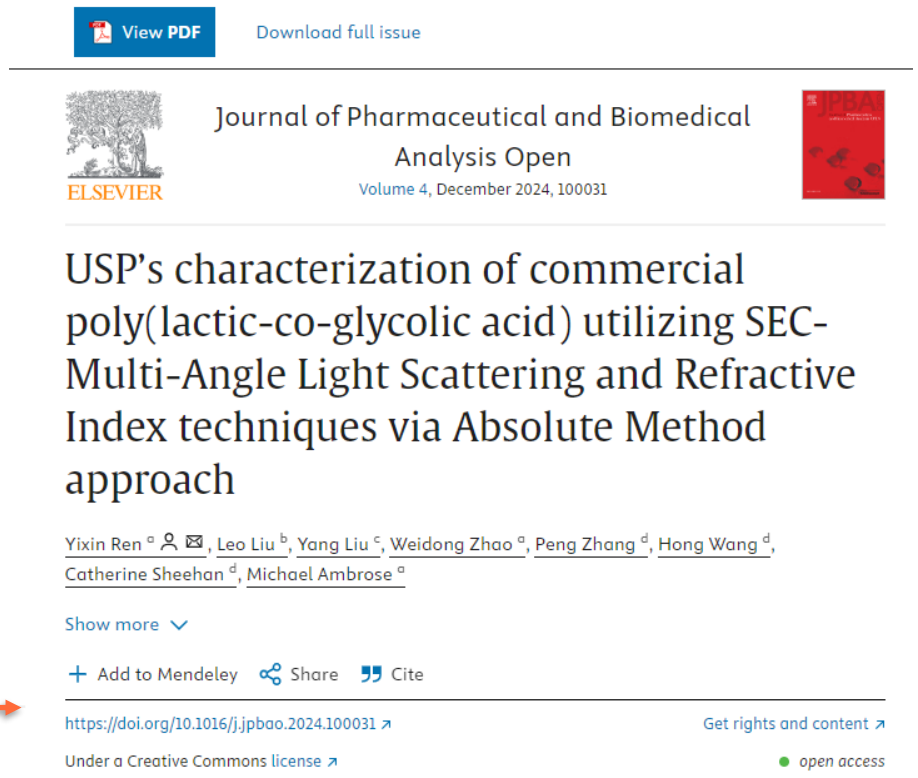
Emerging Solution Work

- Collaboration with USP Digital & Innovation (D&I)
  - LG Polymer fellowship program
    - USP's work on characterization of LG polymers using SEC-MALS and RI via absolute method approach in Journal of Pharmaceutical and Biomedical Analysis Open (JPBA Open).
  - Continuing the research proposed in the fellowship program through collaboration among D&I, USP lab, and USP Excipient group.
  - Exploring new technologies and methodologies, such as Dynamic light scattering (DLS), MALDI-TOF, and NMR Diffusion Ordered Spectroscopy (DOSY).
  - Helping address challenges faced in the method development at the USP lab.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Journal of Pharmaceutical and Biomedical Analysis Open

Volume 4, December 2024, 100031

USP's characterization of commercial poly(lactic-co-glycolic acid) utilizing SEC-Multi-Angle Light Scattering and Refractive Index techniques via Absolute Method approach

Yixin Ren [a], Leo Liu [b], Yang Liu [c], Weidong Zhao [a], Peng Zhang [d], Hong Wang [d], Catherine Sheehan [d], Michael Ambrose [a]

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