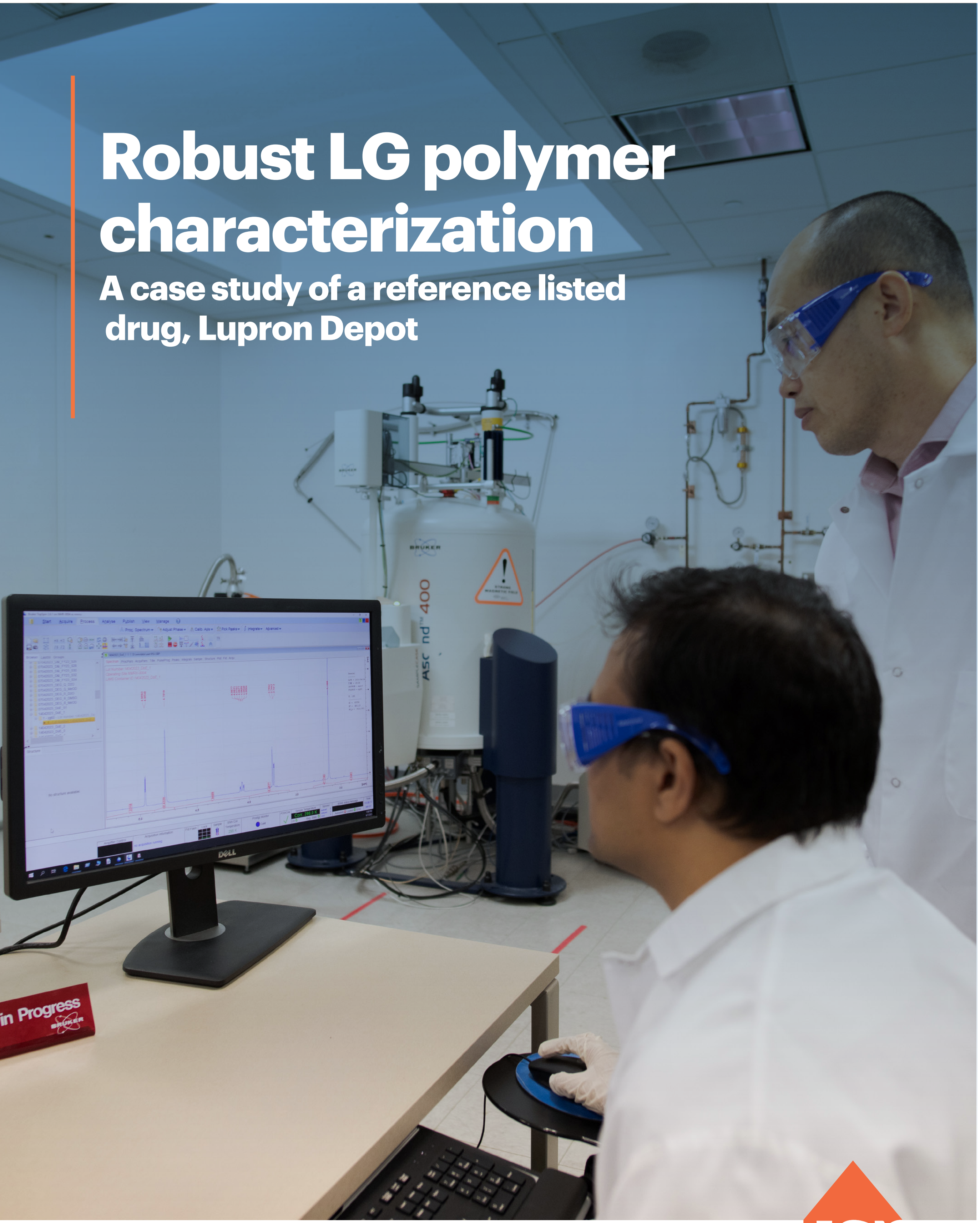
Case study

Robust LG polymer characterization

A case study of a reference listed drug, Lupron Depot



Introduction

Lactide (or lactic acid) and glycolide (or glycolic acid) (LG) polymer is a biodegradable and biocompatible polymer that is widely used in the pharmaceutical, biomedical, and medical device industries (1,2). It is a polyester made from lactide (or lactic acid) and glycolide (or glycolic acid) monomers.

The biodegradation of LG polymer is facilitated by hydrolysis of the ester bonds in the copolymer backbone, yielding lactic and glycolic acids. These byproducts are nontoxic and are metabolized easily by the body. LG polymer is synthesized either by ring-opening polymerization of the cyclic dimers of glycolic acid and lactic acid or by polycondensation of these monomers (1). LG polymer product applications include long-acting microparticles, in situ–forming gels, and solid implants (3).

Various types of LG polymers with different molecular weights, end group (acid / ester), L:G ratio, and molecular structure (linear or branched) have been used in the approved products. LG polymers used in most clinical products are linear, however, one product, Sandostatin® LAR depot (4), is made of a branched LG polymer known as star-LG polymer, a glucose core with attached LG polymer chains (Glu-LG polymer). LG polymer formulations have been used to deliver small and large molecules (peptides and proteins) for extended periods ranging from 1 week to 6 months.

In 1989, the FDA approved Lupron Depot, the first LG polymer-based drug product. Since then, the FDA has approved 24 LG polymer-based branded drug products. Table 1 shows the approved LG polymer-based branded drugs and their indications. Additionally, several LG polymer formulations for cancer treatment and extended-release vaccines are currently in development (5,6). A review article summarizes the use of LG polymer-based formulations in nanomedicine for various diseases, including cancer, neurological diseases, cardiovascular diseases, and infectious and other diseases (7). According to the same review article, there are currently 37 ongoing clinical trials using LG polymer-based nanomedicines.

The advantages of long-acting formulations include improved patient compliance and convenience as well as a lower dose of drug relative to the daily oral regimen, resulting in decreased toxicity. Despite 30 years of research and development, there are only 25 FDA-approved products based on LG polymers, primarily due to the challenges in the manufacturing process, difficulties in predicting in vivo drug efficacy relative to in vitro release, and lack of clear molecular understanding of LG polymers.

Despite the expiration of patent coverage, it was not until 2023 that the FDA approved the first LG polymer-based generic drug, the generic version of Vivitrol (8). This is largely due to the complexity of both the characterization of the LG polymer and the manufacturing process. For injectable complex products such as LG polymer-based drug products, the generic product should be qualitatively (Q1) and quantitatively (Q2) identical to the brand or reference listed drug (RLD) to be approved through an ANDA according to the 505(j) pathway (9). The physicochemical characteristics (particle size, morphology, solubility, porosity, and microscopy) and in vitro performance (Q3) also should be comparable to the RLD.

For generic product development, first the RLD or brand product must be fully characterized to understand the LG polymer structure and composition. Comprehensive characterization of the LG polymer RLD or brand product requires several orthogonal advanced analytical methods — such as nuclear magnetic resonance (NMR), Differential scanning calorimetry (DSC), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR), gel permeation chromatography / size exclusion chromatography (GPC / SEC), dynamic light scattering (DLS), transmission electron microscopy (TEM), and others — to understand its molecular structure and composition. The methods should be able to identify L:G ratio, end group, molecular weight, inherent

Figure 1. An LG polymer synthesis example (1)

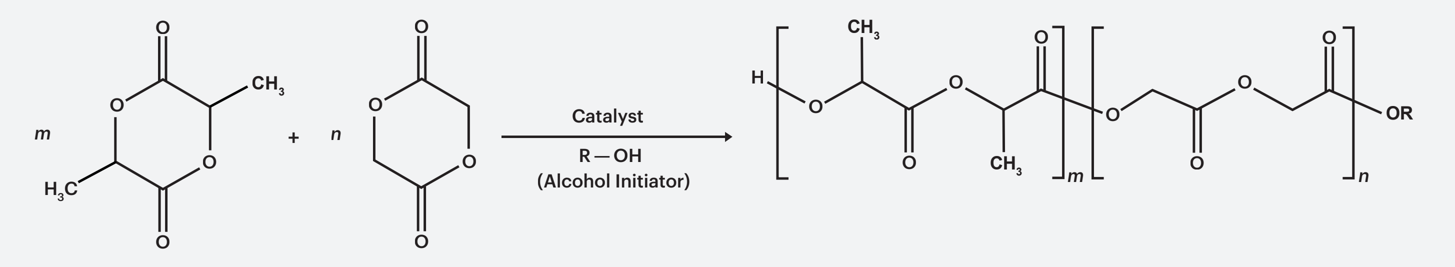


Table 1. LG Polymer-based Injectable Formulations Approved by the US FDA (3, 7, 9-10)

Product Name	API	Duration	Approved	Indication
Lupron Depot	Leuprolide acetate	1, 3, 4, and 6 months	1989, 1996, 1997, 2011	Prostate cancer
Zoladex Depot	Goserlin acetate	1 and 3 months	1989	Prostate cancer, endometriosis, uterine fibroids
Sandostatin LAR	Octreotide acetate	1 month	1998	Metastatic carcinoid tumors
Artidox	Doxycycline hyclate	1 week	1998	Chronic adult periodontitis
Nutropin Depot	Somatotropin	1 month	1999	Long-term treatment of growth failure due to lack of endogenous GH secretion
Trelstar	Triptorelin pamoate	1, 3, and 6 months	2000, 2001, 2010	Palliative treatment of advanced prostate cancer
Arestin	Minocycline HCl	2 weeks	2001	Periodontitis
Eligard	Leuprolide	1, 3, 4, and 6 months	2002	Prostate cancer
Risperidal Consta	Risperidone	2 weeks	2003	Schizophrenia
Vivitrol	Naltrexone	1 month	2006	Opioid and alcohol disorders
Somatuline Depot	Lanreotide	1 month	2007	Long-term treatment of acromegaly
Ozurdex	Dexamethasone	3 months	2009	Inflammation of eye
Propel	Mometasone furoate	1 month	2011	Sinus patency (post-surgery)
Lupron Depot-PED®	Leuprolide acetate	1 month	2011	Central precocious puberty
Bydureon	Exenatide	1 week	2012	Diabetes
Lupaneta Pack	Leuprolide acetate and norethindrone acetate	1 and 3 months	2012	Endometriosis
Bydureon® Pen	Exenatide	1 week	2014	Type 2 diabetes
Signifor LAR	Pasireotide	1 month	2014	Cushing's disease and acromegaly
Bydureon Bcise®	Exevatide	1 week	2017	Type 2 diabetes
Triptodur	Triptorelin pamoate	6 months	2017	Central precocious puberty
Zilretta	Triamcinolone acetoamide	3 months	2017	Osteoarthritis knee pain
Sublocade	Buprenorphine	1 month	2017	Opioid addiction
Sinuva	Mometasone furoate	3 months	2017	Nasal polyps
Perseris	Risperidone	1 month	2018	Schizophrenia
Fensolvi®	Leuprolide acetate	6 months	2020	Central precocious puberty

viscosity, polymer architecture, particle size, porosity, glass transition temperature, and LG polymer synthetic process, as described in Section 2.

LG Polymer Characterization Methods for Analyzing the RLD / Brand Product

Identification of LG Polymer Manufacturing Technology

The identification of LG polymer manufacturing technology involves conducting a block length test using carbon-13 nuclear magnetic resonance (13C NMR) on the extracted LG polymer from the drug product and in-house LG polymer. This test is instrumental in determining the synthetic manufacturing technique of the LG polymer, either polycondensation polymerization or ring-opening polymerization based on the obtained glycolide-glycolide block length value. A lower value is characteristic of polycondensation polymerization, while a higher value indicates ring-opening polymerization. The block length is a critical parameter influencing the polymer architecture and subsequently affecting the drug-release profile of the LG polymer.

Identification of Monomer Ratio of LG Polymer

The monomer ratio for an LG polymer is determined through examination of the extracted LG polymer using quantitative proton (1H) NMR. This analytical method plays a pivotal role in establishing the monomer ratio, a critical parameter influencing the drug release profile. Quantifying the proton signals in the NMR spectrum can precisely ascertain the proportions of lactide (or lactic acid) and glycolide (or glycolic acid) in the polymer. Achieving a monomer ratio consistent with the RLD is critical for ensuring similarity in drug release profiles. This approach not only aids in quality control but also contributes to the reproducibility and consistency of LG polymer-based formulations.

Identification of Polymer End Groups

The identification of polymer end groups is a crucial aspect of characterizing LG polymer. This is achieved through a combination of acid number measurement and 13C NMR analysis. The acid number measurement is particularly reliable in identifying the presence of acid groups in the terminal chains of the polymer. A higher acid number indicates a higher prevalence of acid groups, offering insights into the nature of the end groups.

Although 13C NMR analysis is a valuable tool for end-group identification, it is associated with low sensitivity. Despite this limitation, 13C NMR analysis complements acid number testing by providing additional confirmation of the end group characteristics. In the case of ester end groups, 13C NMR analysis can reveal signals corresponding to aliphatic ester peaks. This dual approach ensures a comprehensive understanding of the end group composition in LG polymer, contributing to the precision and accuracy of polymer characterization. For low-molecular-weight LG polymers, 1H NMR analysis can also be performed for end-group identification.

Identification of Polymer Architecture

Determining equivalency in polymer architecture involves employing various techniques, with 13C NMR playing a central role. Peak-to-peak matching in 13C NMR spectra of the extracted polymer and in-house polymer products provides crucial information regarding the polymer architecture, distinguishing between linear and branched structures of the polymer. Additionally, the presence of carbon peaks attributed to small molecules containing hydroxyl groups can indicate the formation of branched polymers resembling glucose moieties.

Another valuable technique for confirming polymer architecture is measuring T1 and T2 relaxation delays by NMR. Consistent results with similar gradient programs further confirm the similarity in polymer architecture. Use of 4D GPC has proven to be instrumental in demonstrating the branch number similarity between the extracted and in-house products. These comprehensive analytical approaches collectively contribute to the thorough identification and understanding of polymer architecture, aiding researchers in pharmaceutical development and ensuring the quality and consistency of polymer-based formulations.

Molecular Weight and Distribution

Molecular weight and molecular weight distribution were determined through GPC analysis of extracted LG polymer and in-house LG polymer samples. The similarity of the molecular weights and molecular weight distributions of these polymers indicates consistency in the product.

Additionally, the equivalence of the inherent viscosity of both polymers further substantiates the uniformity of the product.

The Crystal Property and Glass Transition Temperature

The crystal property and glass transition temperature (Tg) of LG polymer are influenced by the ratio of D-lactide (or D-lactic acid) to L-lactide (or L-lactic acid) in its composition. A higher proportion of L-lactide (or L-lactic acid) tends to induce crystallinity in the polymer, while a 50:50 ratio of D and L isomers results in an amorphous structure. The crystal property of the polymer affects solubility parameters and particle size of microspheres. Aligning the Tg and x-ray diffractogram with the extracted LG polymer ensures consistency in material behavior and processing characteristics.

Comparative Analysis of Polymer Structure using NMR and IR Spectroscopy

Recording spectroscopic data such as infrared (IR) 1H NMR and 13C NMR spectra under similar conditions facilitates the comparison of structural similarity between an extracted LG polymer and in-house LG polymer. Analysing spectral data allows for a comprehensive assessment of their structural equivalence, enabling the formulator to validate the authenticity and equivalence of the extracted LG polymer to the in-house counterpart.

Case Study – Lupron Depot®

Sample Preparation

To obtain LG polymer samples, the marketed product was dissolved in chloroform at a ratio of 1:10 (w/v) to ensure optimal solubility. Following complete dissolution of the polymer, the solution was filtered to remove undissolved components. Subsequently, the filtrate was subjected to vacuum distillation to evaporate the chloroform.

Characterization of the Extracted LG polymer

The extracted LG polymer from Lupron Depot was subjected to various methods of analysis, which included 1H NMR, 13C NMR, IR, GPC, XRD, and DSC.

Based on the 13C NMR data, the LG polymer used in the Lupron Depot was estimated to be a DL-lactic acid and glycolic acid copolymer with a ratio of 75:25 (*Figure 5*). Further, the GPC results indicated that the weight-average molecular weight of the LG polymer was 13,583 (*Figure 8*). 13C NMR data also revealed that the LG copolymer has an acid end group. With this initial data, a standard LG copolymer with L:G ratio of 75:25 with a nominal molecular weight of 14,000 and with an acid as its end group was chosen to compare the analytical data with the LG polymer extracted from Lupron Depot. The analytical results of the various experiments are shown in *Figures 2–13*.

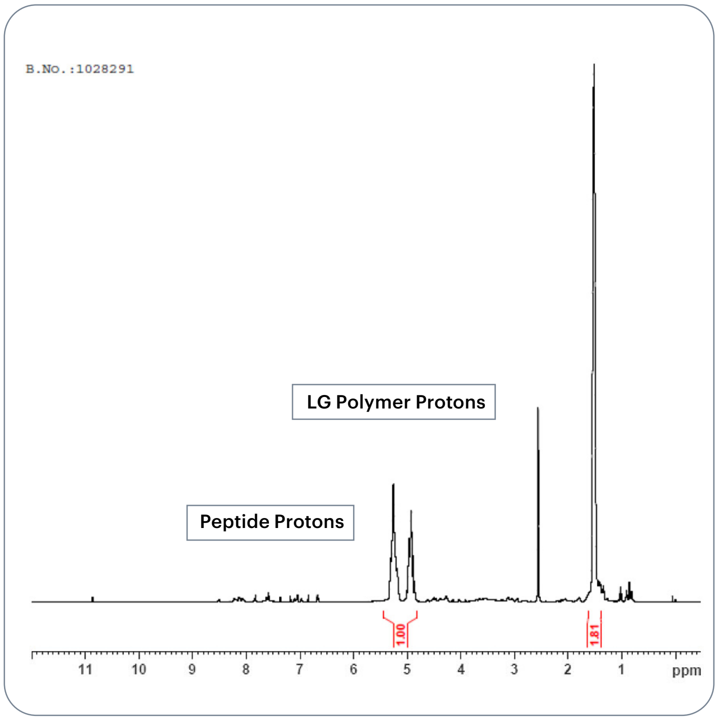


Figure 2. 1H NMR spectra of RLD in deuterated dimethyl sulfoxide (DMSO-D_6) (without extraction)

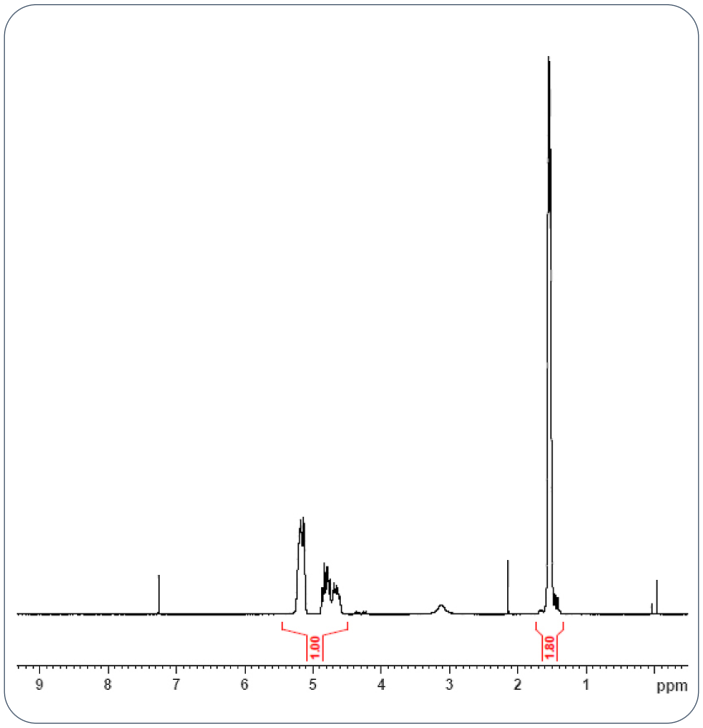


Figure 3. 1H NMR spectra of extracted LG polymer from RLD in deuterated chloroform ($CDCl_3$)

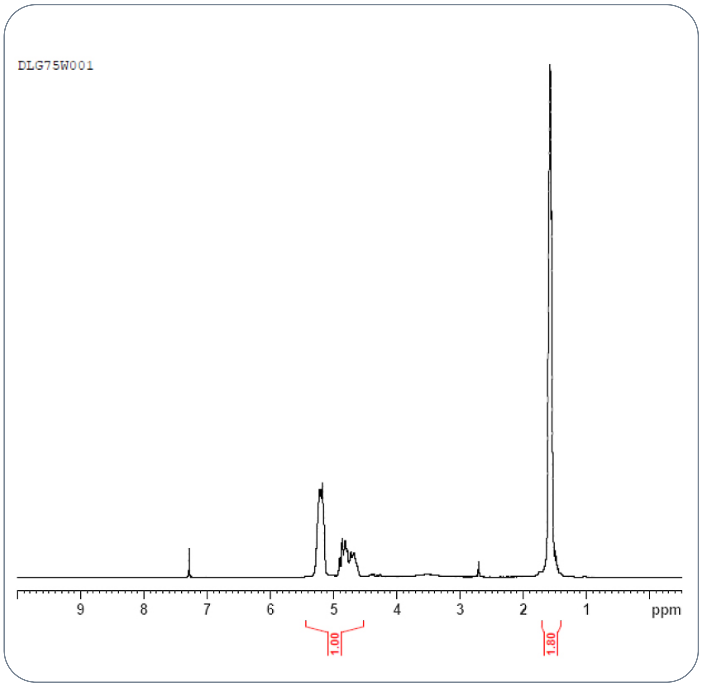


Figure 4. 1H NMR spectra of in-house LG polymer standard in $CDCl_3$

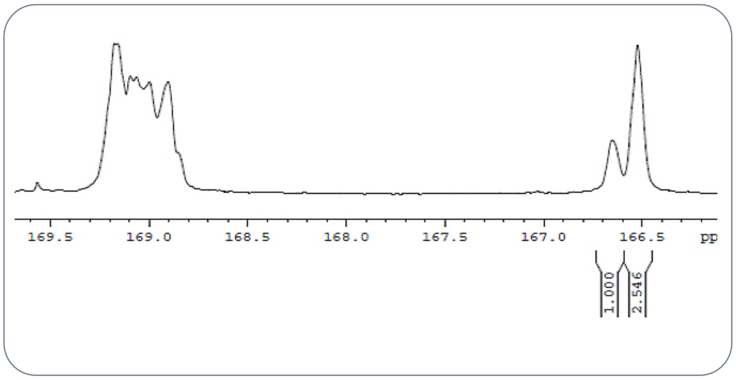


Figure 5. 13C NMR spectra of extracted LG polymer from RLD in DMSO-D_6

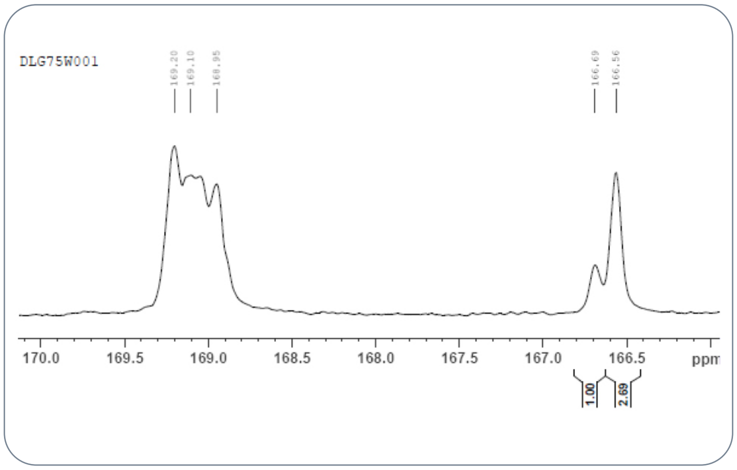


Figure 6. 13C NMR spectra of in-house LG polymer standard in DMSO-D_6

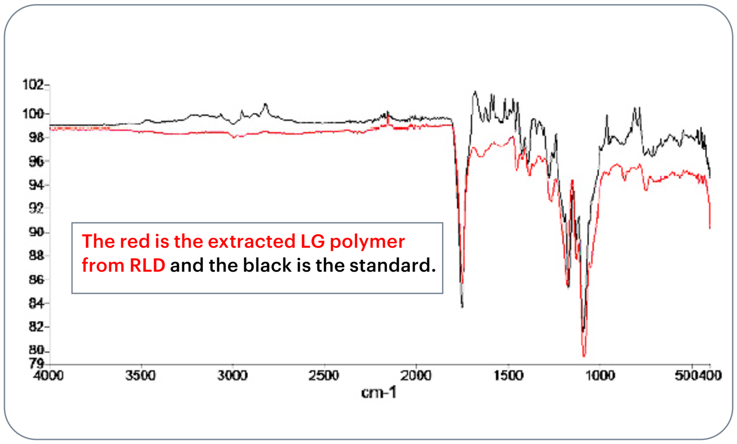
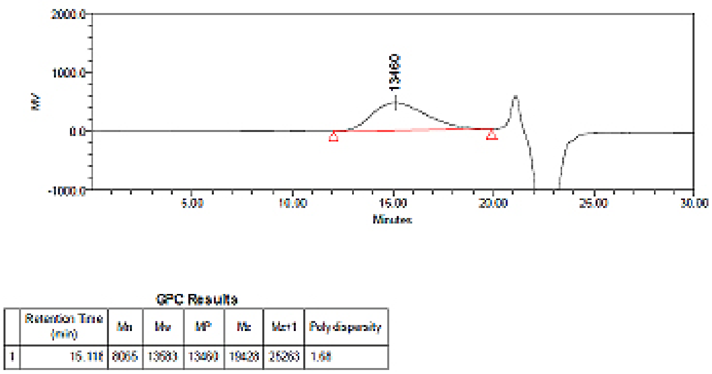


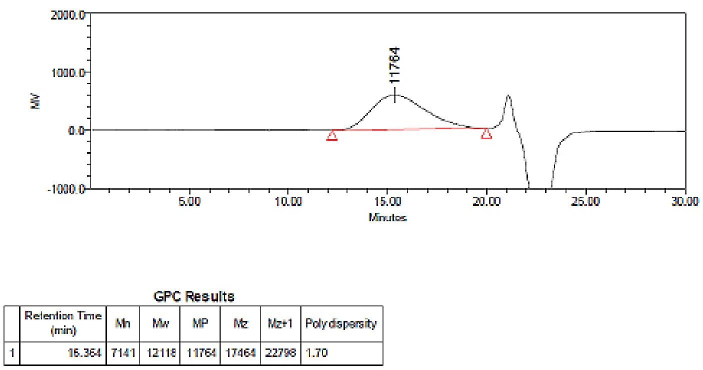
Figure 7. IR spectral comparison of the extracted LG polymer from the RLD with in-house LG polymer standard



GPC Results

	Retention Time (min)	Mn	Mw	MP	Mz	Mz+1	Poly dispersity
1	15.118	8065	13583	13460	19428	25263	1.68

Figure 8. GPC chromatogram for the extracted LG polymer from the RLD



GPC Results

	Retention Time (min)	Mn	Mw	MP	Mz	Mz+1	Poly dispersity
1	16.364	7141	12118	11764	17464	22798	1.70

Figure 9. GPC chromatogram for the in-house LG polymer standard

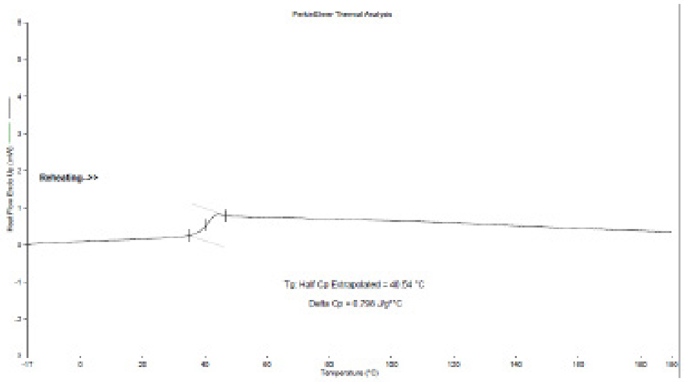


Figure 10. Glass transition temperature by DSC for the extracted LG polymer from the RLD

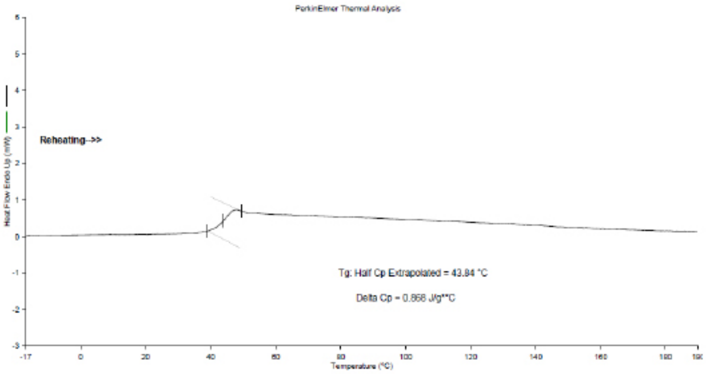


Figure 11. Glass transition temperature by DSC for the in-house LG polymer standard

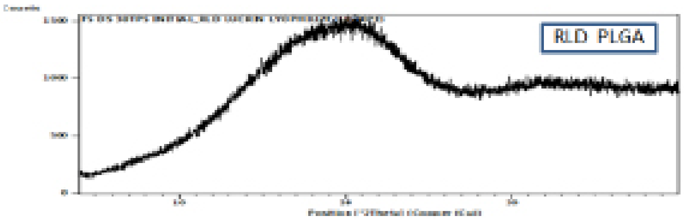


Figure 12. X-Ray diffractogram of extracted LG polymer from the RLD

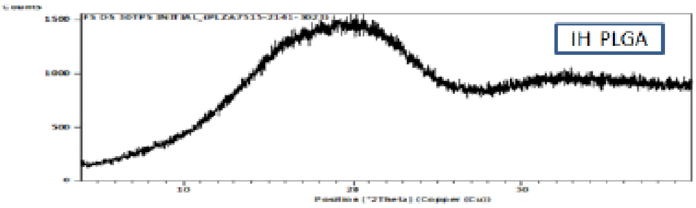


Figure 13. X-Ray diffractogram of in-house LG polymer standard

Summary of Findings

Based on the data obtained from the various characterization methods, the comparison between the in-house LG polymer and the RLD from the analysis of Lupron Depot has provided valuable insights into the formulation characteristics and performance attributes of both materials.

Through comprehensive analysis and experimentation, the extracted LG copolymer from the Lupron Depot was found to match with the LG copolymer standard with an L:G ratio of 75:25, a molecular weight of approximately 14,000, and an acid end group (*Table 2*).

USP aims to emphasize that the exacted LG polymer from the formulation may not be identical to the raw material LG polymer used during the formulation. This discrepancy can be attributed primarily to the alterations that can occur in the LG polymers during the formation process.

USP LG Polymer Compendial Standards and Reference Standards

During an FDA and USP joint workshop on complex excipients in February 2017, the FDA emphasized the importance of advancing the science of excipient quality testing and selection (11). The FDA also encouraged drug product innovation, underlining the value of excipient function to drug product performance and equivalence. Two scientific presentations from the FDA revealed the challenges in the analytical testing evaluation of LG polymer-based drugs (12-13). USP Excipient Expert Committees have established an LG Polymer Joint Subcommittee to develop compendial standards for LG polymers as a priority area.

Table 2. Comparison between In-House LG Polymer and the exacted LG Polymer from the RLD

Test	In-House LG Polymer (DLG75W001)	The extracted LG Polymer from the RLD (Lupron Depot 7.5 mg)
Appearance	white powder	white powder
Monomer ratio (DL-lactic acid: Glycolic acid)	75:25	75:25
Inherent viscosity	0.17 dL/g	0.18 dL/g
Molecular weight (Mw)	12,118 Da	13,583 Da
Polydispersity (PD)	1.70	1.68
Block length	1.37	1.39
Polymorph	amorphous	amorphous
TG	43.84° C	40.54° C
Acid number	11.8 mg KOH/g	10.2 mg KOH/g
NMR	confirms with the chemical structure	confirms with the chemical structure
IR	Consistent with extracted LG polymer from RLD	

The LG polymers in the FDA's Global Substance Registration System (GSRS)* include:

- DL-Lactide and Glycolide (50:50) Copolymer 12000 Acid
- DL-Lactide and Glycolide (50:50) Copolymer 15000 Acid
- DL-Lactide and Glycolide (50:50) Copolymer 30000 Acid
- DL-Lactide and Glycolide (50:50) Copolymer 46000 Acid
- DL-Lactide and Glycolide (50:50) Copolymer 63000 Acid
- DL-Lactide and Glycolide (50:50) Copolymer 7500 Ethyl Ester
- DL-Lactide and Glycolide (50:50) Copolymer 12000 Ethyl Ester
- DL-Lactide and Glycolide (50:50) Copolymer 22000 Lauryl Ester
- DL-Lactide and Glycolide (50:50) Copolymer 64000 Lauryl Ester
- DL-Lactide and Glycolide (55:45) Copolymer 70000 Acid
- DL-Lactide and Glycolide (75:25) Copolymer 9500 Acid
- DL-Lactide and Glycolide (75:25) Copolymer 20000 Acid
- DL-Lactide and Glycolide (75:25) Copolymer 140000 Acid
- DL-Lactide and Glycolide (75:25) Copolymer 9500 Methyl Ester
- DL-Lactide and Glycolide (80:20) Copolymer 27000 Acid
- DL-Lactide and Glycolide (85:15) Copolymer 23000 Acid
- POLYGLACTIN 370
- POLYGLACTIN 910
- POLYLACTIDE
- POLYLACTIDE (14000 MW)
- POLYLACTIDE (23000 MW)
- POLYLACTIDE (0.4 DL/G)
- LAURYL POLYLACTIDE (14000 MW)
- POLYLACTIDE, L-

*https://gsrs.ncats.nih.gov/ginas/app/beta/home

Table 3: Current Status and Next Steps

Type of document	Item #	Date	*PF* issue	Title	Release or proposed new USP 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	Monograph will become official in USP-NF 2025 Issue 1 in May 2025 (to be released to the publication in December 2024); RS has 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	
General chapter	1	2024/09	50 (5)	<315> NMR number-average molecular weight determination for LG polymers	NA	Prospectus: https://www.uspnf.com/notices/gc-315-prospectus-20231229
	2	2024/09	50 (5)	<316> GPC molecular weight and polydispersity determination for LG polymers using universal calibration	NA	Prospectus: https://www.uspnf.com/notices/gc-316-prospectus-20231229

USP Analytical Reference Materials

In addition to developing several monographs and their associated RS and general chapters, USP is considering to offer several other LG polymers (as shown in section 4) as analytical reference materials (ARMs) that could be used to identify the type of LG polymer that was used in the several approved RLD / brand products for which no generics are available.

USP proposes a naming system for the LG polymer ARMs. This naming system includes five segments:

1. Polymer type acronym

Co- or homopolymer	Manufacturing process	Acronym
Copolymer	Ring-opening	PLG
	Polycondensation	PLGA
Homopolymer	Ring-opening	PL or PG
	Polycondensation	PLA or PGA

2. Ratio of two numbers (percentage is probably the most accepted) separated by a colon, e.g., 75:25.
3. Acronym for the monomers. When ‘A’ denotes acid, the manufacturing process refers to lactic acid/glycolic acid polycondensation; otherwise, it refers to lactide/glycolide ring-opening polymerization:

Monomer	Acronym
racemic lactide	DLL
racemic lactic acid	DLLA
L-lactide	LL
L-lactic acid	LLA
glycolide	G
glycolic acid	GA

4. Viscosity: A number (probably one digit) loosely related to the molecular weight.
5. Terminal: E for ester and A for acid.

Table 4. USP's Proposed ARM Products

USP Description	CAS #	Molecular Formula	Molecular Weight	IUPAC Name	Viscosity
PLG 75:25 DLLG 5E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	43,000 – 63,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.50 – 0.70 dL/g
PLG 75:25 DLLG 7E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	76,000 – 115,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.71 – 1.00 dL/g
PLG 75:25 DLLG 10A	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	Approx. 150,000 da	Poly(DL-lactide-co-glycolide), acid	0.90 – 1.30 dL/g or 0.80 – 1.20 dL/g
PLG 75:25 DLLG 10E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	Approx. 150,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.80 – 1.20 dL/g
PLG 75:25 DLLG 3A	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	24,000 – 38,000 da	Poly(DL-lactide-co-glycolide), acid terminated	0.32 – 0.44 dL/g
PLG 75:25 DLLG 3E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	24,000 – 38,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.32 – 0.44 dL/g
PLG 75:25 DLLG 9E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	Approx. 140,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.90 – 1.30 dL/g
PLGA 75:25 DLLAGA 2E	34346-01-5	$(C_3H_4O_2)_m \cdot (C_2H_2O_2)_n$	7,000 – 17,000 da	Poly(DL-lactic-co-glycolic acid), ester	0.16 – 0.24 dL/g
PLGA 75:25 DLLAGA 2A	34346-01-5	$(C_3H_4O_2)_m \cdot (C_2H_2O_2)_n$	4,000 – 15,000 da	Poly(DL-lactic-co-glycolic acid), acid terminated	0.14 – 0.22 dL/g
PLG 50:50 DLLG 3A	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	24,000 – 38,000 da	Poly(DL-lactide-co-glycolide), acid terminated	0.32 - 0.44 dL/g
PLG 50:50 DLLG 3E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	24,000 – 38,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.32 - 0.44 dL/g
PLG 50:50 DLLG 4E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	38,000 – 54,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.45 – 0.60 dL/g
PLG 50:50 DLLG 5A	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	54,000 – 69,000 da	Poly(DL-lactide-co-glycolide), acid terminated	0.61 – 0.74 dL/g
PLG 50:50 DLLG 5E	26780-50-7	$(C_6H_8O_4)_m \cdot (C_4H_4O_4)_n$	54,000 – 69,000 da	Poly(DL-lactide-co-glycolide), ester terminated	0.61 – 0.74 dL/g

Conclusions

USP is proactive in offering comprehensive solutions that can help users navigate LG polymer nomenclature and characterization complexities with confidence, ease, and certainty. Our USP experts are actively developing monographs and their associated RS for each of the compendial-eligible LG polymers to help increase the adoption and application of LG polymers. In addition, USP is offering robust Analytical Reference Materials (ARMs) and supporting resources (stimuli articles, technical guides, case studies, etc.) that can assist users in accurately annotating and identifying the LG polymer in the RLD.

The Leuprolide Depot analysis data presented here demonstrates the value of using multiple analysis techniques to characterize LG polymers extracted from an RLD and provide a critical step to advance along the path in the development of generic-equivalent products.

References

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