Complex Sameness:

Tests to Determine Properties for PLGA Excipients in Long-Acting Formulations

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AKiNA

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Akina Overview

- **Research and Development company based in Purdue Research Park**
- **Founded by Professor Kinam Park in 2001**
- **Two major divisions: PolySciTech & Akinalytics**

PolySciTech
Polymers for research (PEG-PLGA, PLCL, PLGA-FL, PLGA-PEG-Mal)

- Over 650 products available
- Over 375 publications using products

Akinalytics
Advanced analytical polymer assays

- Full characterization of PLGA
- Contracted analysis and research

Regulatory: ANDA - bioequivalence

- **Abbreviated New Drug Application (ANDA) for proposed generic product based on a reference listed drug (RLD)**

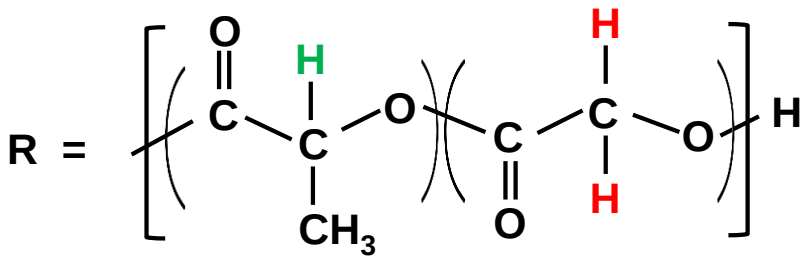
- **Require demonstration of sameness by *in vitro* methods**

Q1:	**Qualitative sameness.**	**Identification of the excipient type**
Q2:	**Quantitative sameness:**	**Identification of the excipient quantity**
Q3μS:	**Microstructural sameness:**	**Identification of the microstructure**

PLGA

Poly(lactide-co-glycolide) (PLGA)

- Has been used since 1970s: OLD!
- Properties:
  - Lactide:Glycolide (L:G) Ratio
  - Molecular weight / Distribution
  - End-cap
  - Randomness versus blockiness in glycolide distribution
  - Molecular shape
  - Chirality



Lactic acid Glycolic acid

Assays must be performed on the final product formulation approved by the FDA

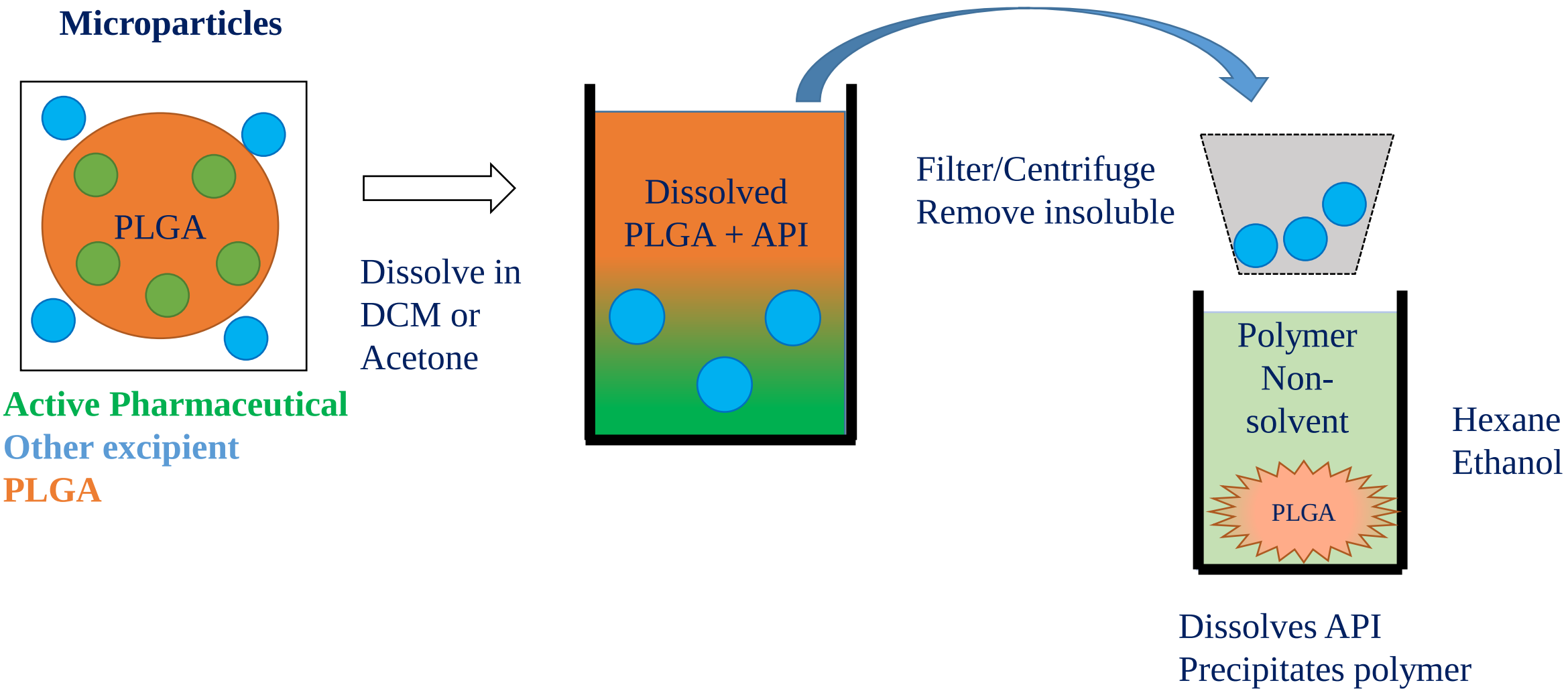
Clinical Products using PLGA

Akinalytics
know your polymer

Product Name	API*	Type	Duration	Dose	Approved
Lupron Depot®	Leuprolide acetate	Microparticle	1,3,4,6 months	7.5 mg/month	1989, 1996, 1997,2011
Zoladex® Depot	Goserelin acetate	Solid implant	1,3 months	3.6 mg/month	1989
Sandostatin® LAR	Octreotide acetate	Microparticle	1 month	10-30 mg/month	1998
Atridox®	Doxycycline hyclate	In situ gel*	1 week	42.5 mg/week	1998
Nutropin Depot®	Somatotropin	Microparticle	1 month	13.5 mg/month	1999
Trelstar®	Triptorelin pamoate	Microparticle	1,3,6 months	3.75 mg/month	2000, 2001, 2010
Somatuline® Depot	Lanreotide	Microparticle	1 month	60 mg/month	2000
Arestin®	Minocycline HCl	Microparticle	2 weeks	0.5 mg/week	2001
Eligard®	Leuprolide	In situ gel**	1,3,4,6 months	7.5 mg/month	2002
Risperidal® Consta®	Risperidone	Microparticle	2 weeks	12.5 mg/week	2003
Vivitrol®	Naltrexone	Microparticle	1 month	380 mg/month	2006
Ozurdex®	Dexamethasone	Solid implant	3 months	0.23 mg/month	2009
Propel®	Mometasone furoate	Solid implant	1 month	0.37 mg/month	2011
Bydureon®	Exenatide	Microparticles	1 week	2.0 mg/week	2012
Lupaneta Pack™	Leuprolide acetate	Microparticles	3 months	3.75 mg/month	2012
Signifor® LAR	Pasireotide	Microparticles	1 month	20~60 mg/month	2014
Zilretta®	Triamcinolone acetoamide	Microparticles	3 month	32 mg/3 months	2017
Sublocade™	Buprenorphine	In situ gel	1 month	100, 300 mg/month	2017
Perseris™	Risperidone	In situ gel	1 month	90, 120 mg/month	2018

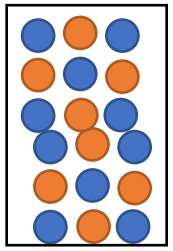
To date, no generic LAI formulation has been approved in USA.

PLGA: Sample Extraction



PLGA: Advanced Extraction

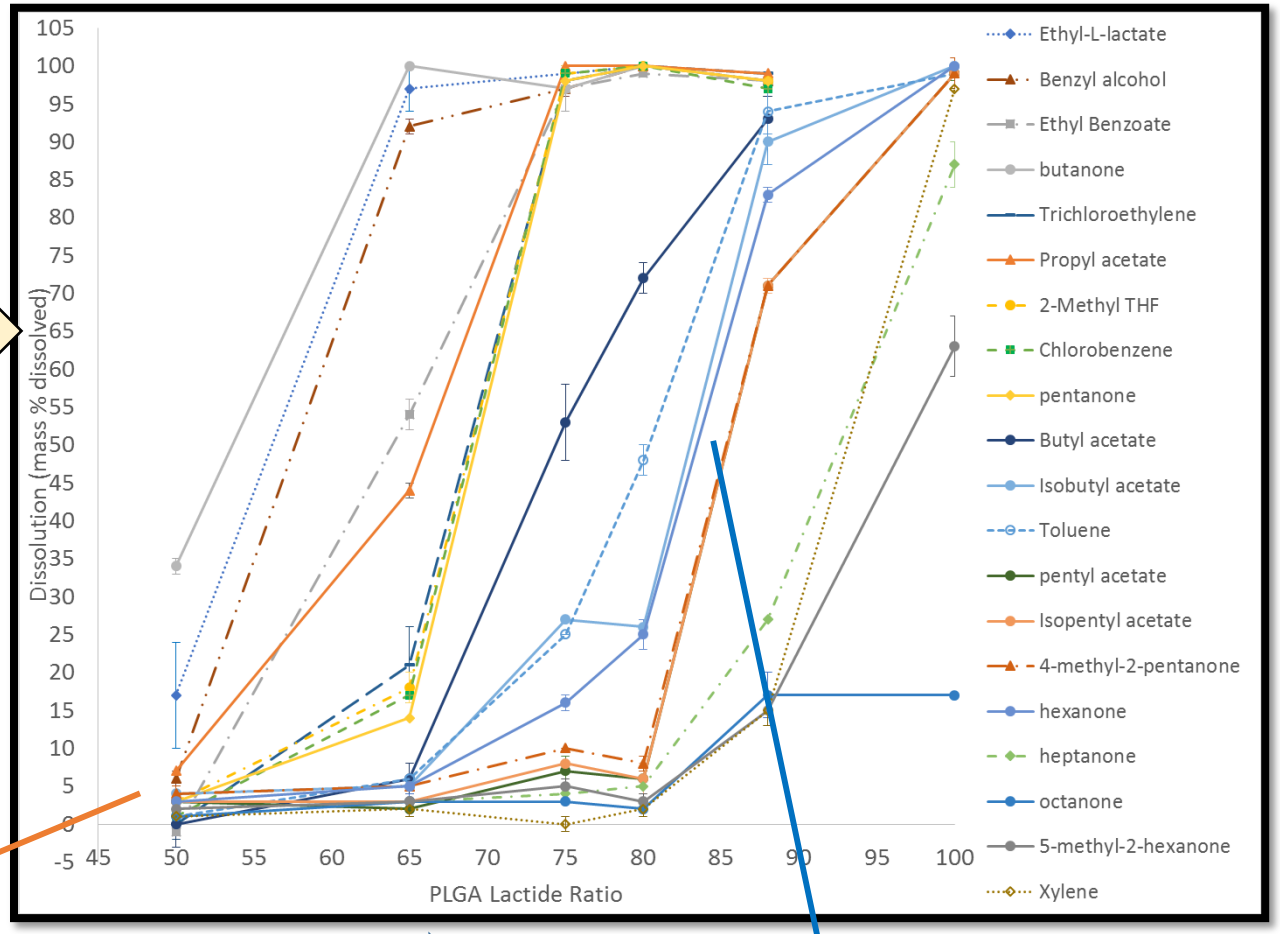
Formulation woth Mixed PLGAs



Semi-solvent separation

High-Lactide PLGA

Low-Lactide PLGA



Scientific Poster Presentation has more details.

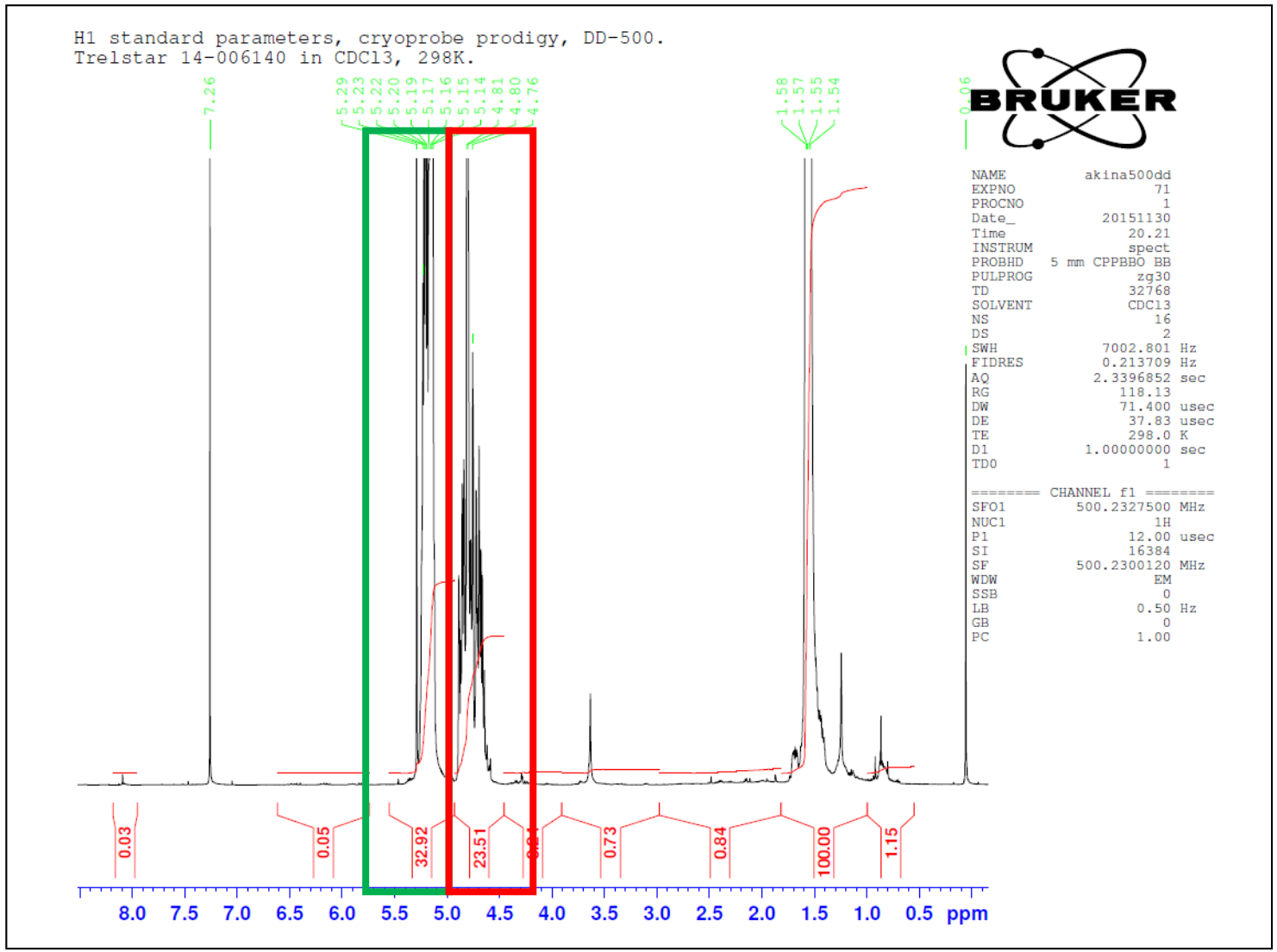
Semi-solvents: Low-Lactide PLGAs are insoluble.

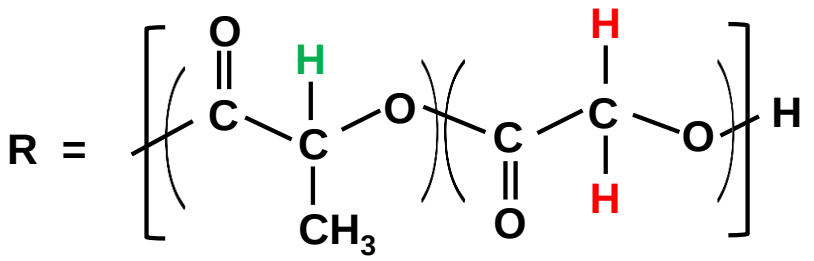
Lactoselective Solubility

Semi-solvent: High-Lactide PLGA are soluble.

Skidmore, Sarah, Justin Hadar, John Garner, Haesun Park, Kinam Park, Yan Wang, and Xiaohui Jiang.
Complex sameness: Separation of mixed poly (lactide-co-glycolide) s based on the lactide: glycolide ratio. *Journal of Controlled Release* 30 (2019) 174-184.

PLGA: L:G ratio by ^{1}H NMR



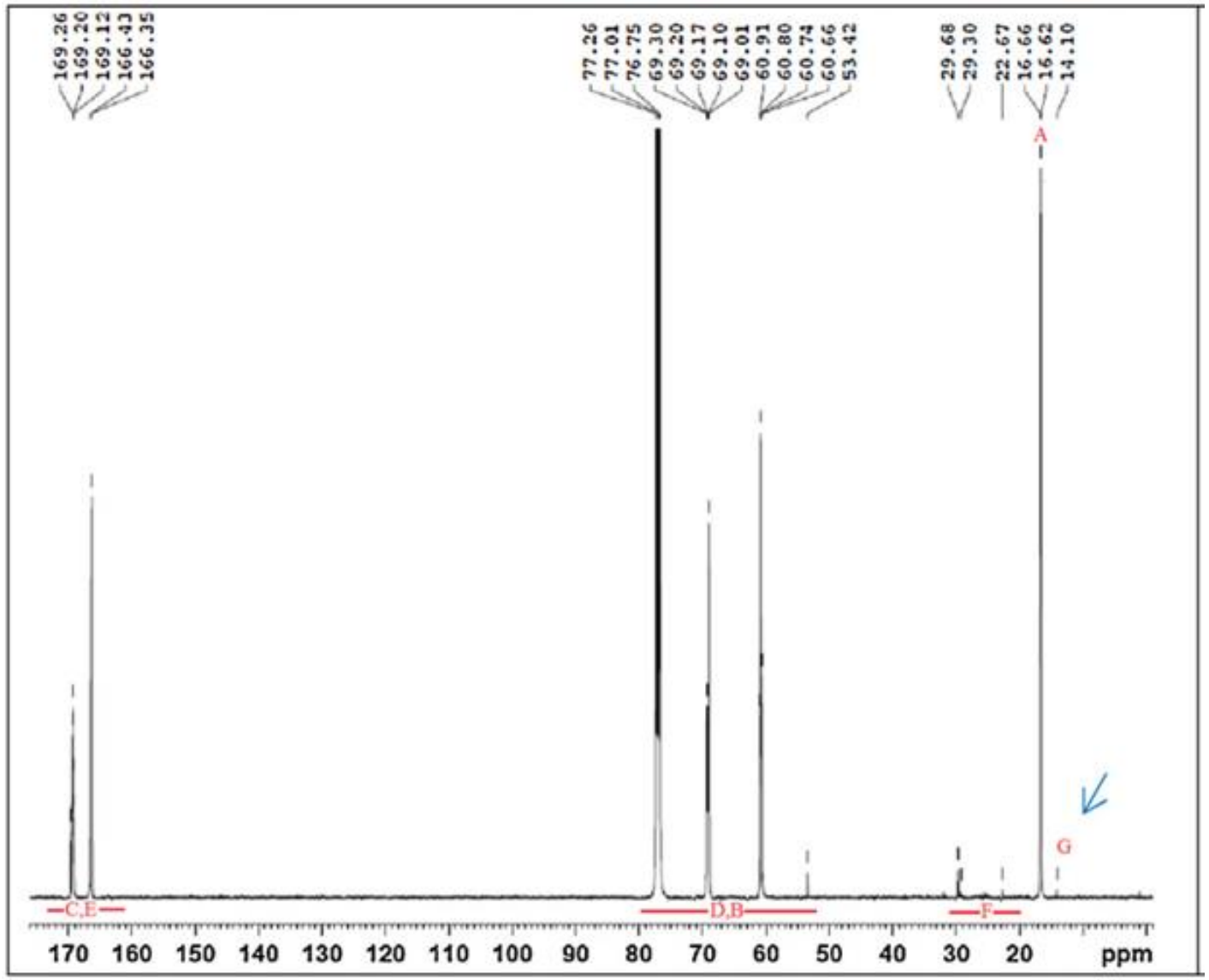


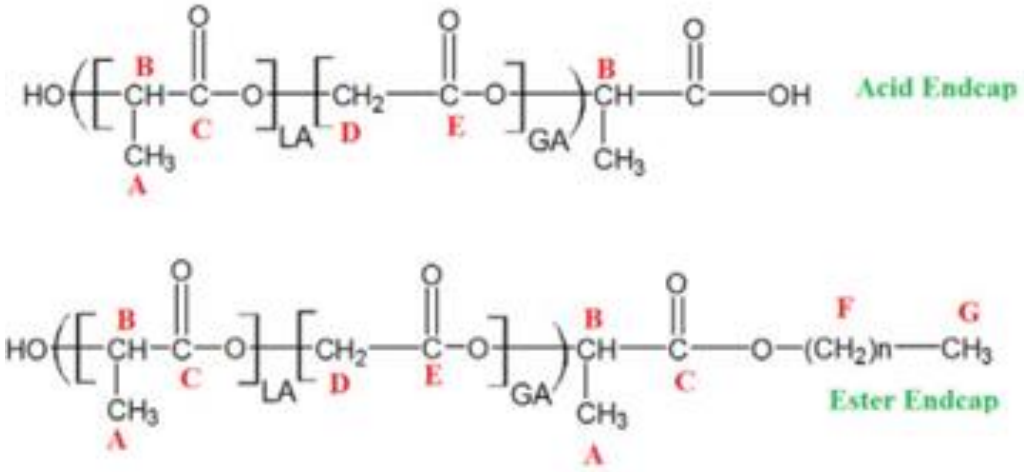
Lactic acid Glycolic acid

$$M_L = P_L/(P_L + (P_G/2))$$
$$M_G = (P_G/2))/(P_L + (P_G/2))$$

- L:G ratio is critical to the degradation kinetics.
- Higher L:G ratio degrades more slowly

PLGA: Endcap by ^{13}C NMR

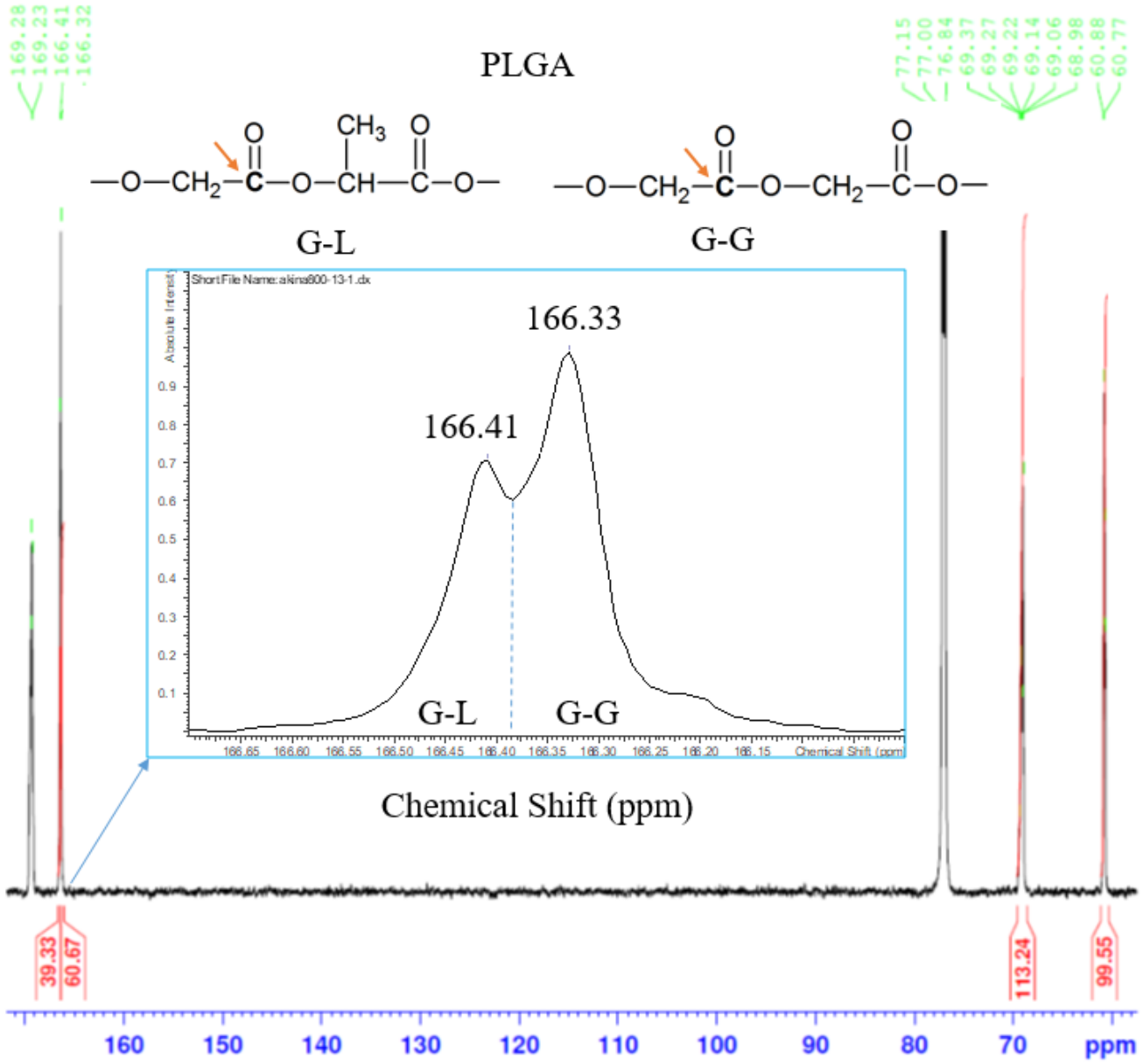




- Requires extremely clean sample (alkanes can give false positive)
- High number of scans required for high Signal/Noise

John Garner, Skidmore, Sarah, Haesun Park, Kinam Park, Stephanie Choi, Yan Wang,
A protocol for assay of poly(lactide-co-glycolide) in clinical products. Int. J. Pharm. 495 (2015) 87-92.

PLGA: Blockiness



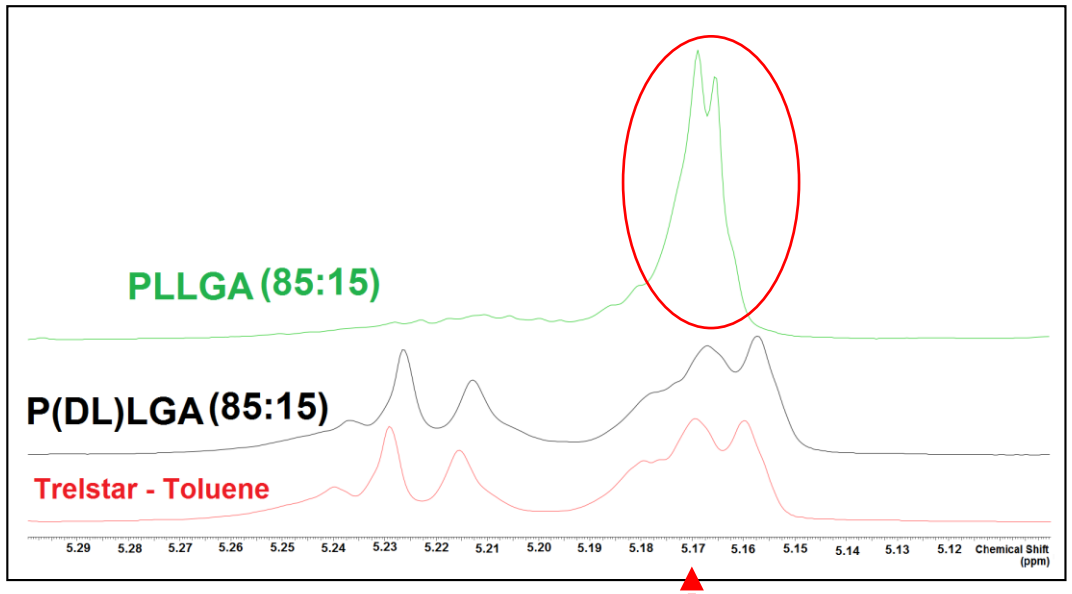
- L:G react at different rates
- Not uniformly ‘random’ but reaction method affects distribution
- ‘Sameness’ or just quality?

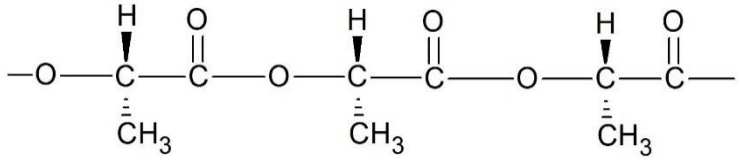
- Rcms = GL/GG (Hausberger)
- Rc = GG/GL (Skidmore)

1. Hausberger, Angela G., and Patrick P. DeLuca. Characterization of biodegradable poly (D, L-lactide-co-glycolide) polymers and microspheres. J. Pharm. Biom. Anal. 13(6) (1995): 747-760.

2. Skidmore, Sarah, Justin Hadar, John Garner, Haesun Park, Kinam Park, Yan Wang, and Xiaohui Jiang. Complex sameness: Separation of mixed poly (lactide-co-glycolide) s based on the lactide: glycolide ratio. Journal of Controlled Release 30 (2019) 174-184.

PLGA: Chirality





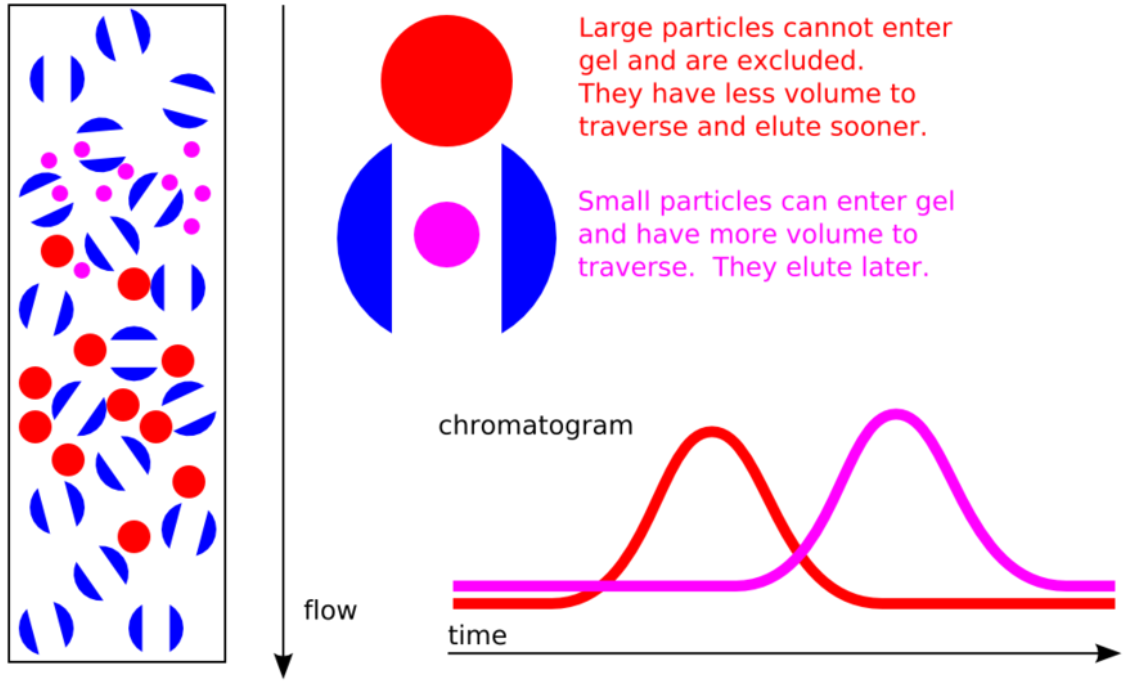
isotactic (~ 5.17 ppm)

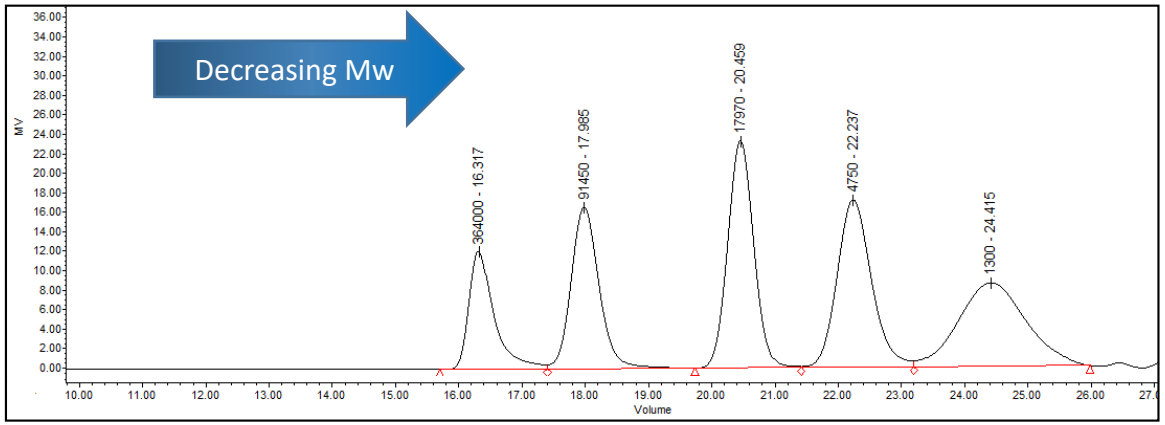
- Running HNMR with decoupling (1) separates isotactic lactide (5.17 ppm) from other lactide forms (atactic, syndiotactic, ~5.2-5.3 ppm)
- For PLGA 75:25 or greater, can distinguish P(DL)LG from PLLG. A lower lactide content has a substantial glycolide interference.

Scientific Poster Presentation has more details.

1. Zell, Mark T., Brian E. Padden, Amanda J. Paterick, Khalid AM Thakur, Robert T. Kean, Marc A. Hillmyer, and Eric J. Munson. Unambiguous determination of the 13C and 1H NMR stereosequence assignments of polylactide using high-resolution solution NMR spectroscopy. Macromolecules 35 (2002) 7700-7707.

PLGA: MW by GPC-ES (External Standard)

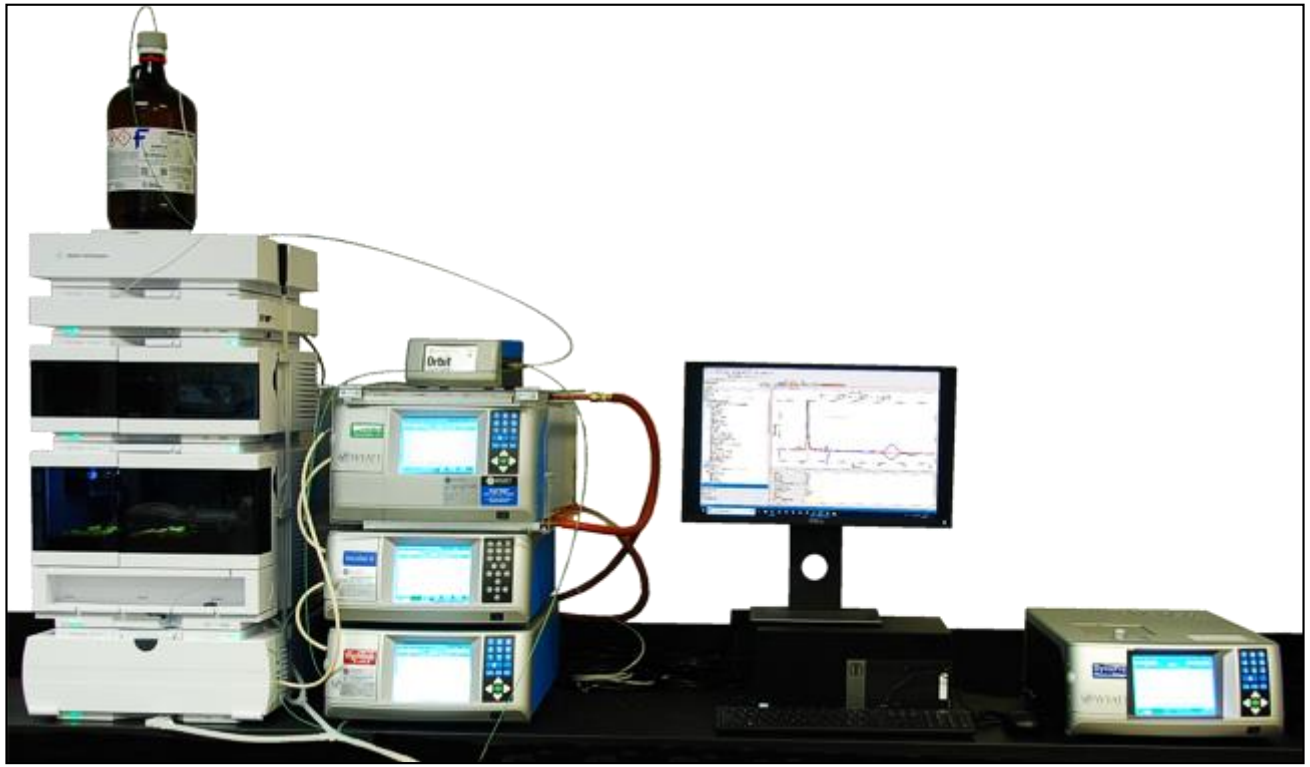




Polystyrene Standards (1ml/min THF)

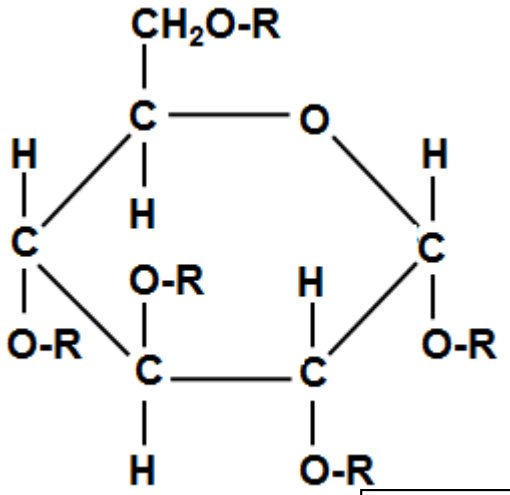
- Size-exclusion chromatography/Gel-permeation chromatography separate based on the hydrodynamic volume
- Solvation between polymer/solvent, interaction with column also controls the retention time.
- Non-representative standard (typically polystyrene) and the lack of standardized methods mean lab-to-lab differences in GPC measured Mw.

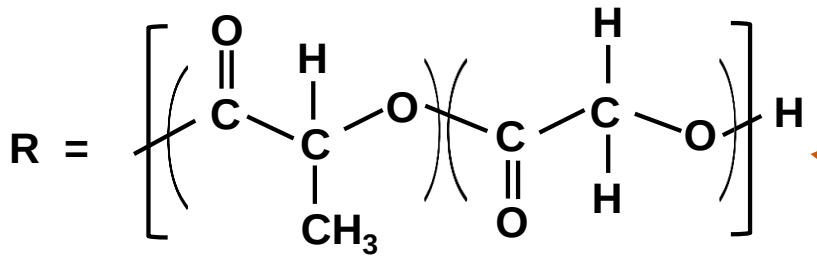
PLGA: MW by GPC-4D



- GPC separation followed by MALLS (Rg, Mw), Viscometry (intrinsic viscosity), in-line dynamic light scattering (R_h), and refractive index (concentration).
- Universal calibration, no external standards, no solvation-artifacts
- Light-scattering is better for low-RI solvents (acetone) than high-RI solvents (THF)
- In-depth information about PLGA for determination of molecular shape & branching.

PLGA: Branching Units/Molecule of Sandostatin®





or R = H

Polymer (*dn/dc*)	Average Branch Units	Branch Units at M_w	Branch Units at M_n	M_n (GPC-4D)	M_w (GPC-4D)	Viscosity at M_n (mL/g)	$R_h(Q)$ at M_n (nm)	$R_h(V)$ at M_n (nm)
Glu-PLGA (Sandostatin 66-1) (0.0980 mL/g)	3.11 ± 0.18	3.07 ± 0.14	2.89 ± 0.18	37,743 ± 510	44,437 ± 816	32.78 ± 0.39	4.80 ± 0.91	5.76 ± 0.05
Glu-PLGA (Sandostatin 66-2) (0.0980 mL/g)	3.10 ± 0.09	3.04 ± 0.009	2.83 ± 0.09	37,211 ± 365	43,683 ± 416	32.74 ± 0.43	4.90 ± 0.74	5.72 ± 0.04
Glu-PLGA (Sandostatin 10) (0.0980 mL/g)	3.25 ± 0.18	3.07 ± 0.31	2.85 ± 0.41	36,676 ± 1020	43,012 ± 856	32.19 ± 0.75	4.77 ± 0.56	5.67 ± 0.09
Glu-PLGA (Sandostatin 28) (0.0980 mL/g)	3.18 ± 0.20	2.75 ± 0.37	2.55 ± 0.49	39,063 ± 1561	46,473 ± 1248	33.97 ± 1.72	5.11 ± 0.82	5.83 ± 0.15

- Sandostatin lists Glucose-PLGA-Glucose without any specific information on branching.
- GPC-4D branched-PLGA method was developed/validated using a series of standards.
- Tested Sandostatin extract: branching average typically ranges between ~ 2.5-4 branching units/molecule.

Hadar, Justin, Sarah Skidmore, John Garner, Haesun Park, Kinam Park, Yan Wang, Bin Qin, and Xiaohui Jiang. "Characterization of branched poly (lactide-co-glycolide) polymers used in injectable, long-acting formulations." *Journal of Controlled Release* (2019).

PLGA: Different PLGAs in Trelstar® 22 mg

Semi-solvents for Lacto-selective Solubility

- Simple extraction – NMR only gives average LA:GA of components

Order	Extraction Solvent	L:G Ratio of PLGA[1]	Mass of PLGA (mg)	% of Total PLGA	R_c[1]	Weight average Mol Wt (Da)[2]	Number average Mol Wt (Da)[2]	PDI[2]
1	Xylenes	84.0:16.0	9.3	6.3	0.342	17,552 ± 333	15,616 ± 266	1.124 ± 0.002
2	Isopentyl acetate	82.9:17.1	24.8	16.4	0.425	28,339 ± 60	24,568 ± 113	1.148 ± 0.003
3	Toluene	82.9:17.1	37.3	24.6	0.464	51,260 ± 81	45,027 ± 189	1.138 ± 0.004
4	n-Butyl acetate	74.3:25.7	19.3	12.7	0.802	26,121 ± 184	22,690 ± 179	1.151 ± 0.001
5	2-Pentanone	72.6:27.4	22.0	14.5	0.874	37,178 ± 90	32,489 ± 171	1.144 ± 0.004
6	Butanone	70.9:29.1	38.2	25.2	1.00	55,256 ± 430	49,312 ± 408	1.120 ± 0.003
	Butanone residual	70.9:29.1	0.5	0.3	[1] NMR			
Total: 151.4 mg				100.0%	[2] GPC-4D			

- Trelstar 6-month comprised of multiple PLGA-types.
- Semi-solvent extraction enables separating out each specific type (L:G ratio) of PLGA and analyzing the specific fraction independently.

Skidmore, Sarah, Justin Hadar, John Garner, Haesun Park, Kinam Park, Yan Wang, and Xiaohui Jiang. Complex sameness: Separation of mixed poly (lactide-co-glycolide) s based on the lactide: glycolide ratio. *Journal of Controlled Release* 30 (2019) 174-184.

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Advanced Analytical Techniques for Mixed Polymer Drug-Delivery Systems

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Development of hydrogel-based in vitro dissolution apparatus for microparticle formulations

The content of this presentation is of the authors and does not necessarily represent the official views of the Food and Drug Administration.

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