

Analysis of the branch units of glucose-poly(lactide-co-glycolide) in Sandostatin® LAR formulation

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Introduction

Glucose-poly(lactide-co-glycolide) (Glu-PLGA) is a star-shape, branched polymer used in Sandostatin® LAR, an injectable, long-acting formulation of octreotide. The number of branches (or arms) of the Glu-PLGA is a critical characteristic of the polymer. Currently, no literature report is available focusing on determining the number of branches of the Glu-PLGA used in Sandostatin® LAR. Such characterization is important for quality control, as well as for developing generic products which need to match the reference listed drug for qualitative and quantitative (Q1/Q2) sameness of the Glu-PLGA, including the presence of glucose and the branch units per molecule. The purpose of this study is to fully characterize the Glu-PLGA extracted from Sandostatin® LAR using a gel permeation chromatography (GPC) equipped with four detectors (GPC-4D) consisting of in-line multi-angle light-scattering, refractive index, dynamic-light scattering, and viscometric analysis.

Methods

A sample of Sandostatin® LAR (Novartis, 30 mg) was reverse engineered by dissolution in dichloromethane, filtration, and reprecipitation in hexane followed by vacuum drying. The extracted PLGA was analyzed using the GPC-4D system with an acetone mobile phase as described previously [1]. The method was validated with a series of known branched PLGA standards which were compared against a linear PLGA of similar molecular weight and the lactide:glycolide (L:G) ratio. The molecular weight was also assayed by osmometer in acetone with a molecular weight cut off 20 kDa membrane (Gonotec).



Figure 1. Images from Sandostatin LAR® extraction process. Sample showing vial of material used to extract PLGA and hexane precipitated PLGA extract after centrifugation.

Results

The results of characterization of Glu-PLGA extracted from three different Sandostatin® LAR lots are listed in Table 1. The branch units per molecule of Glu-PLGA varied between 2.5 to 3.5 when measured against a linear PLGA having the branch units of 2 per molecule (Figure 2). The number-average molecular weight (M_n) measured by an osmometer is $39,306 \pm 6,071$ Da ($n=3$), which is in agreement with the GPC results (Table 2). A dn/dc of 0.0980 mL/g was used for software calculation based on most similar polymer which dn/dc was determined at the time of analysis. These values were reported in the current publication [2] (data presented in red in Table 2). Subsequent batch measurement of dn/dc for GLU-PLGA from Sandostatin® LAR Lot 356510 was determined to be 0.0984 ± 0.0001 mL/g ($n=3$) (data presented in black in Table 2).

Table 1. Characterization of Glu-PLGA extracted from Sandostatin® LAR using GPC-4D. All data presented as average \pm standard deviation. (η : intrinsic viscosity; $R_h(Q)$: radius determined by dynamic light scattering detector; $R_h(V)$: radius determined by viscosity; MHS: Mark-Houwink-Sakurada, $n=3$).

Polymer (dn/dc)	Average Branch Units	Branch Units at M_w	Branch Units at M_n	M_n (GPC-4D)	M_w (GPC-4D)	η at M_n (mL/g)	$R_h(Q)$ at M_n (nm)	$R_h(V)$ at M_n (nm)	MHS
Glu-PLGA (Sandostatin 66-1) (0.0980 mL/g)*	3.11 ± 0.18	3.07 ± 0.14	2.89 ± 0.18	$37,743 \pm 510$	$44,437 \pm 816$	32.78 ± 0.39	4.80 ± 0.91	5.76 ± 0.05	0.457 ± 0.013
	3.03 ± 0.18	3.00 ± 0.14	2.81 ± 0.18	$37,800 \pm 575$	$44,703 \pm 975$	33.05 ± 0.67	4.75 ± 0.59	5.75 ± 0.06	0.470 ± 0.012
	3.10 ± 0.09	3.04 ± 0.09	2.83 ± 0.09	$37,211 \pm 365$	$43,683 \pm 416$	32.74 ± 0.43	4.90 ± 0.74	5.72 ± 0.04	0.459 ± 0.016
Glu-PLGA (Sandostatin 66-2) (0.0980 mL/g)*	3.03 ± 0.09	2.96 ± 0.09	2.75 ± 0.09	$37,281 \pm 362$	$43,681 \pm 423$	32.87 ± 0.43	4.90 ± 0.74	5.72 ± 0.04	0.463 ± 0.017
	3.25 ± 0.18	3.07 ± 0.31	2.85 ± 0.41	$36,676 \pm 1,020$	$43,012 \pm 856$	32.19 ± 0.75	4.77 ± 0.56	5.67 ± 0.09	0.458 ± 0.018
	3.19 ± 0.18	3.03 ± 0.31	2.81 ± 0.41	$37,584 \pm 1,602$	$43,802 \pm 1,556$	32.98 ± 1.67	4.72 ± 0.58	5.74 ± 0.18	0.456 ± 0.018
Glu-PLGA (Sandostatin 10) (0.0980 mL/g)*	3.18 ± 0.20	2.75 ± 0.37	2.55 ± 0.49	$39,063 \pm 1,561$	$46,473 \pm 1,248$	33.97 ± 1.72	5.11 ± 0.82	5.83 ± 0.15	0.433 ± 0.051
	3.14 ± 0.02	2.71 ± 0.37	2.50 ± 0.49	$39,452 \pm 1,669$	$46,719 \pm 1,580$	34.42 ± 2.07	5.02 ± 0.73	5.86 ± 0.20	0.434 ± 0.051
	3.10 ± 0.08	2.93 ± 0.15	2.72 ± 0.15	$38,164 \pm 865$	$44,726 \pm 1,404$	33.33 ± 0.73	4.85 ± 0.14	5.77 ± 0.06	0.456 ± 0.016
Glu-PLGA (Sandostatin 28) (0.0980 mL/g)*	3.16 ± 0.07	2.98 ± 0.16	2.78 ± 0.16	$37,673 \pm 1,024$	$45,151 \pm 1,749$	32.92 ± 0.75	4.90 ± 0.15	5.75 ± 0.07	0.452 ± 0.013
	3.10 ± 0.08	2.93 ± 0.15	2.72 ± 0.15	$38,164 \pm 865$	$44,726 \pm 1,404$	33.33 ± 0.73	4.85 ± 0.14	5.77 ± 0.06	0.456 ± 0.016
	3.10 ± 0.08	2.93 ± 0.15	2.72 ± 0.15	$38,164 \pm 865$	$44,726 \pm 1,404$	33.33 ± 0.73	4.85 ± 0.14	5.77 ± 0.06	0.456 ± 0.016
Overall Averages (0.0980 mL/g)*	3.16 ± 0.07	2.98 ± 0.16	2.78 ± 0.16	$37,673 \pm 1,024$	$45,151 \pm 1,749$	32.92 ± 0.75	4.90 ± 0.15	5.75 ± 0.07	0.452 ± 0.013
(0.0984 mL/g)*	3.10 ± 0.08	2.93 ± 0.15	2.72 ± 0.15	$38,164 \pm 865$	$44,726 \pm 1,404$	33.33 ± 0.73	4.85 ± 0.14	5.77 ± 0.06	0.456 ± 0.016

Table 2. Comparison of Osmometer data to GPC-4D data for indicated polymers.

Polymer	M_w (GPC-4D)	M_n (GPC-4D)	Osmometer M_n ($n = 4$)
3-Arm PLGA (Akina Product 229)	$42,010 \pm 177$	$36,714 \pm 115$	$39,464 \pm 3,129$
4-Arm PLGA (Akina Product 227)	$44,869 \pm 395$	$39,496 \pm 438$	$43,513 \pm 1,174$
6-Arm PLGA (Akina Product 228)	$49,375 \pm 269$	$46,715 \pm 281$	$51,879 \pm 5,569$
Glu-PLGA (Purchased from Corbion)	$52,148 \pm 84$	$40,985 \pm 48$	$42,440 \pm 2,093$
Glu-PLGA (Purchased from Evonik)	$52,943 \pm 306$	$40,061 \pm 466$	$43,339 \pm 2,195$
Glu-PLGA (Purchased from Lactel)	$55,049 \pm 171$	$42,469 \pm 289$	Not Tested
Glu-PLGA (Sandostatin)	$43,835 \pm 1196$	$37,188 \pm 950$	$39,306 \pm 6,071$

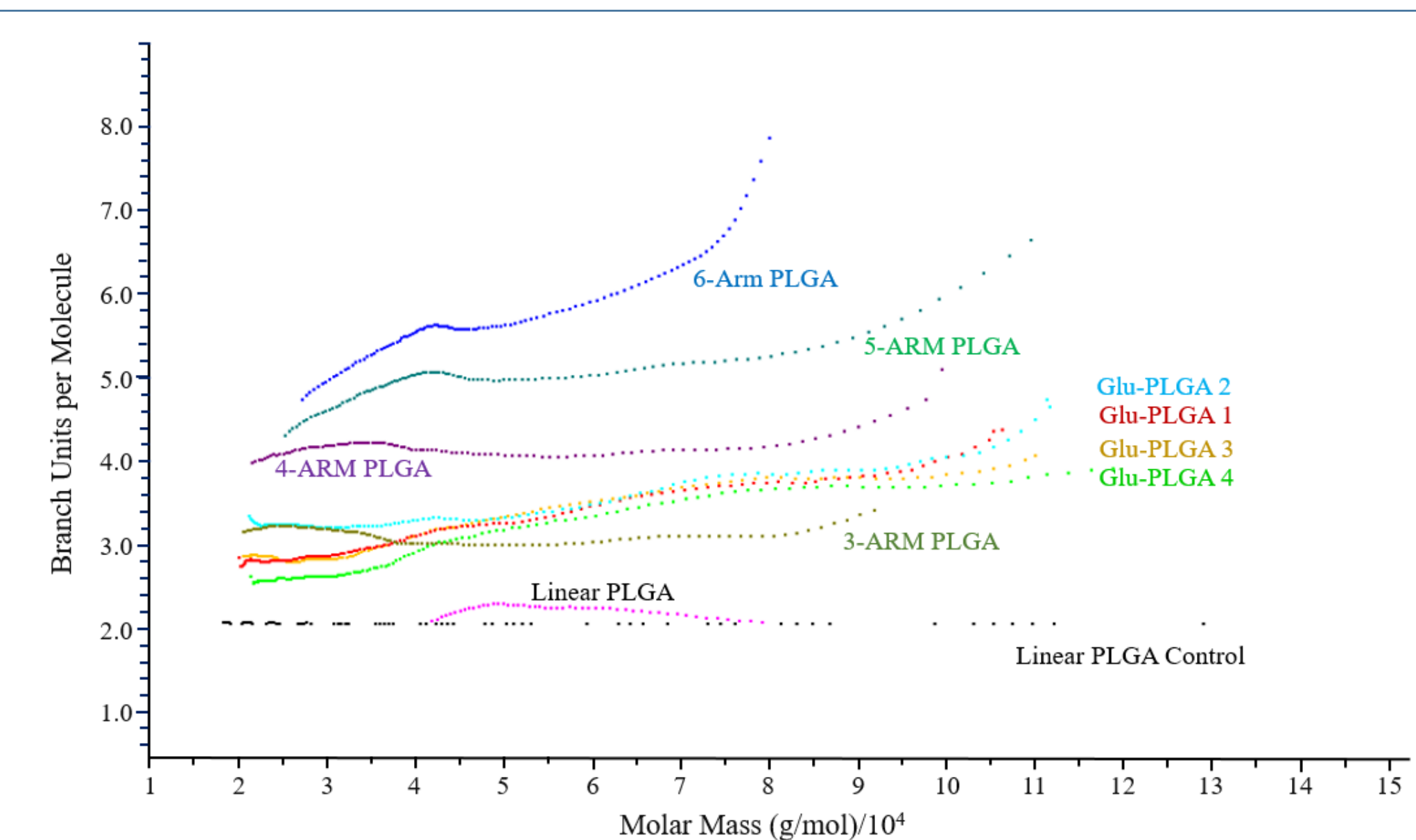


Figure 2. The branch units per molecule as a function of the molar mass of Glu-PLGA. Glu-PLGAs were obtained from three Sandostatin extracts from three different lots (four doses total). The standard branched PLGAs having 3~6 arms were synthesized in-house.

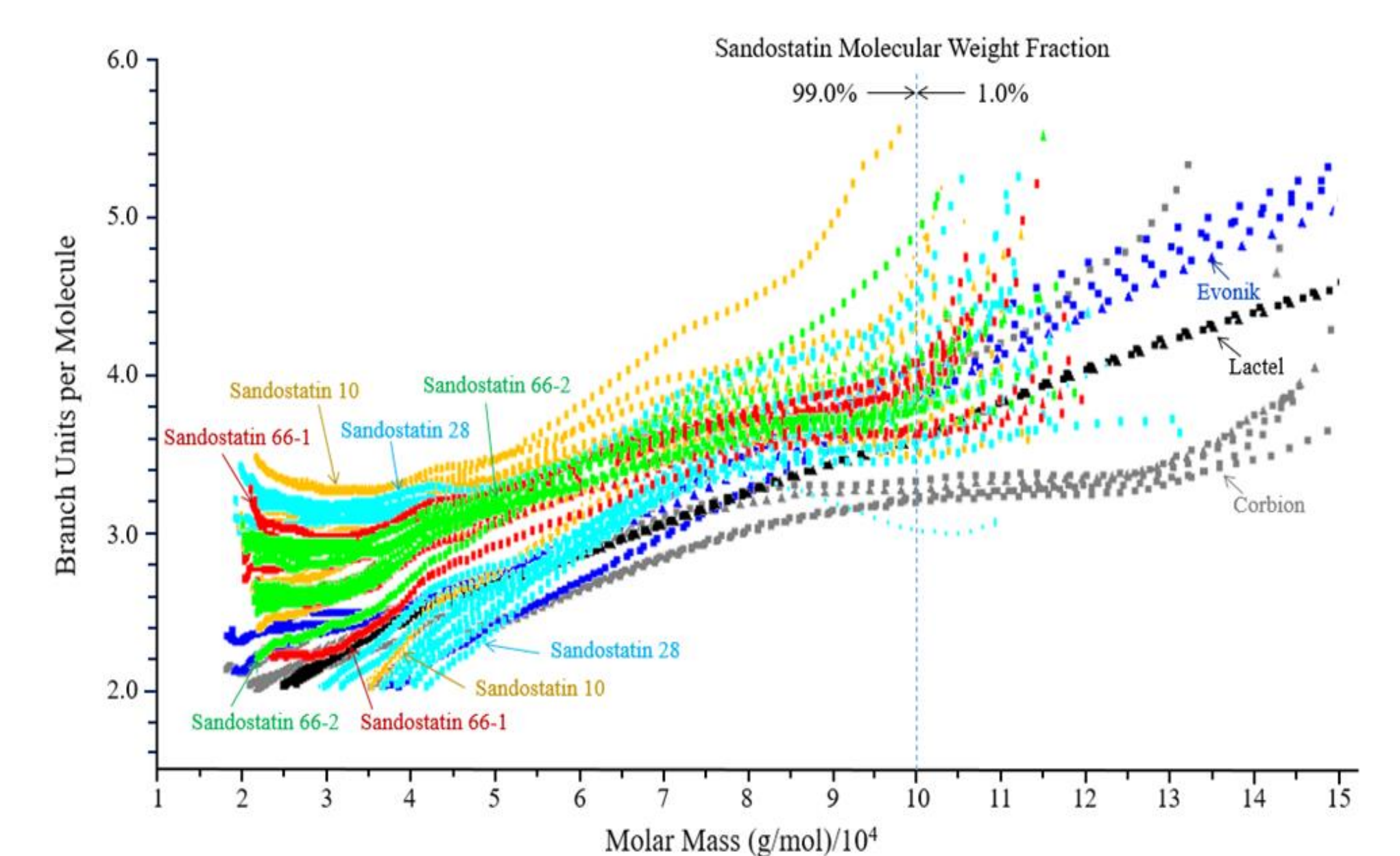


Figure 3. (A) The branch units per molecule as a function of the molar mass of four Sandostatin LAR extracts from 3 different lots (66: 356166; 10: 356510; and 28: 357028), Corbion, Evonik, and Lactel.

Conclusion

The developed GPC-4D methodology enables a thorough characterization of Glu-PLGA extracted from Sandostatin® LAR. This method can be used as a tool for quality control as well as for determining the Q1/Q2 sameness for proposed generic products.

References

- J. Hadar, J. Garner, S. Skidmore, H. Park, K. Park, Y. K. Jhon, Y. Wang. Correlation analysis of refractive index (dn/dc) for PLGAs with different ratios of lactide to glycolide. 2018 Controlled Release Society (CRS) Annual Meeting (2018) Abstract 95.
- J. Hadar, S. Skidmore, J. Garner, H. Park, K. Park, Y. Wang, B. Qin, and X. Jiang. "Characterization of branched poly (lactide-co-glycolide) polymers used in injectable, long-acting formulations." Journal of Controlled Release 304:75-89 (2019).

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