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 ± 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 ± standard deviation. (η: intrinsic viscosity; Rh(Q): radius determined by dynamic light scattering detector; Rh(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)* (0.0984 mL/g)*	3.11 ± 0.18 3.03 ± 0.18	3.07 ± 0.14 3.00 ± 0.14	2.89 ± 0.18 2.81 ± 0.18	37,743 ± 510 37,800 ± 575	44,437 ± 816 44,703 ± 975	32.78 ± 0.39 33.05 ± 0.67	4.80 ± 0.91 4.75 ± 0.59	5.76 ± 0.05 5.75 ± 0.06	0.457 ± 0.013 0.470 ± 0.012
Glu-PLGA (Sandostatin 66-2) (0.0980 mL/g)* (0.0984 mL/g)*	3.10 ± 0.09 3.03 ± 0.09	3.04 ± 0.09 2.96 ± 0.09	2.83 ± 0.09 2.75 ± 0.09	37,211 ± 365 37,281 ± 362	43,683 ± 416 43,681 ± 423	32.74 ± 0.43 32.87 ± 0.43	4.90 ± 0.74 4.90 ± 0.74	5.72 ± 0.04 5.72 ± 0.04	0.459 ± 0.016 0.463 ± 0.017
Glu-PLGA (Sandostatin 10) (0.0980 mL/g)* (0.0984 mL/g)*	3.25 ± 0.18 3.19 ± 0.18	3.07 ± 0.31 3.03 ± 0.31	2.85 ± 0.41 2.81 ± 0.41	36,676 ± 1,020 37,584 ± 1,602	43,012 ± 856 43,802 ± 1,556	32.19 ± 0.75 32.98 ± 1.67	4.77 ± 0.56 4.72 ± 0.58	5.67 ± 0.09 5.74 ± 0.18	0.458 ± 0.018 0.456 ± 0.018
Glu-PLGA (Sandostatin 28) (0.0980 mL/g)* (0.0984 mL/g)*	3.18 ± 0.20 3.14 ± 0.02	2.75 ± 0.37 2.71 ± 0.37	2.55 ± 0.49 2.50 ± 0.49	39,063 ± 1,561 39,452 ± 1,669	46,473± 1,248 46,719 ± 1,580	33.97 ± 1.72 34.42 ± 2.07	5.11 ± 0.82 5.02 ± 0.73	5.83 ± 0.15 5.86 ± 0.20	0.433 ± 0.051 0.434 ± 0.051
Overall Averages (0.0980 mL/g)* (0.0984 mL/g)*	3.16 ± 0.07 3.10 ± 0.08	2.98 ± 0.16 2.93 ± 0.15	2.78 ± 0.16 2.72 ± 0.15	37,673 ± 1024 38,164 ± 865	45151± 1,749 44,726 ± 1,404	32.92 ± 0.75 33.33 ± 0.73	4.90 ± 0.15 4.85 ± 0.14	5.75 ± 0.07 5.77 ± 0.06	0.452 ± 0.013 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 ± 177	36,714 ± 115	39,464 ± 3,129
4-Arm PLGA (Akina Product227)	44,869 ± 395	39,496 ± 438	43,513 ± 1,174
6-Arm PLGA (Akina Product 228)	49,375 ± 269	46,715 ± 281	51,879 ± 5,569
Glu-PLGA (Purchased from Corbion)	52,148 ± 84	40,985 ± 48	42,440 ± 2,093
Glu-PLGA (Purchased from Evonik)	52,943 ± 306	40,061 ± 466	43,339 ± 2,195
Glu-PLGA (Purchased from Lactel)	55,049 ± 171	42,469 ± 289	Not Tested
Glu-PLGA (Sandostatin)	43,835 ± 1196	37,188 ± 950	39,306 ± 6,071

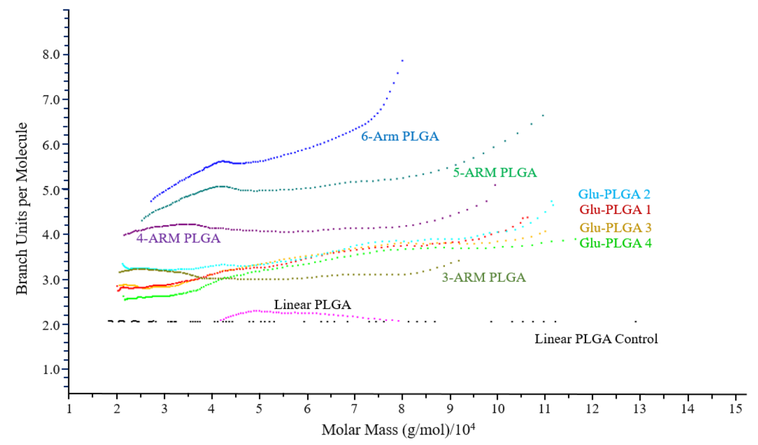

Figure 2. The branch units per molecule as a function of the molar mass of Glu-PLGA. Glu-PLGAs were obtained from three Sandostatin extracts from three different lots (four doses total). The standard branched PLGAs having 3~6 arms were synthesized in-house.

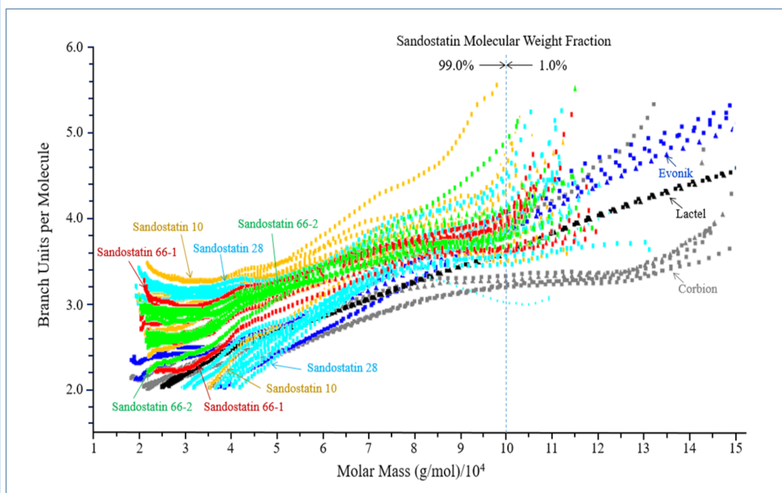

Figure 3. (A) The branch units per molecule as a function of the molar mass of four Sandostatin LAR extracts from 3 different lots (66: 356166; 10: 356510; and 28: 357028), Corbion, Evonik, and Lactel.

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

[1] 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.

[2] 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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