Assay of Clinical Product Long-Term Delivery Systems for PLGA Properties

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Introduction

- Poly(lactide-co-glycolide) (PLGA) is a biodegradable polymer used in a wide variety of clinical products due to its capacity to biodegrade by hydrolysis into non-toxic lactic and glycolic acids.
- There are many different types of PLGA depending on the lactide:glycolide (LA:GA) ratio, endcap, and molecular weight.
- There is no good method established for assaying the PLGA component properties of microparticles used in injectable depot formulations, such as Risperdal® Consta® and Trelstar®.
- Such an assay is necessary for quality control as well as ensuring that proposed generic formulations provide qualitative and quantitative (Q1/Q2) sameness in regards to the reference product.

Purpose of this work is to establish a testing protocol which extracts PLGA from clinically used microparticle formulations and assays it to ensure Q1/Q2 compliance for parental depot formulations.

Methods

- Commercially purchased Risperdal Consta, which is a monthly injection, as well as Trelstar 3.75, 11.25, and 22.5 mg doses (1, 3, and 6 month injections, respectively) were dissolved in dichloromethane (DCM) (**Fig. 1**)
- Solutions filtered and dialyzed for three days (MWCO 6000-8000Da) against organic solvent.
- Subsequently, these solutions were concentrated, and precipitated in a stirring excess of hexane (**Fig. 2**) and dried under deep vacuum.
- The PLGA was then analyzed by gel permeation chromatography (GPC) (**Fig. 3**), ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR (**Fig. 4**). (1)

Figure 1. dissolution of microparticles

Figure 2. Precipitation in hexane

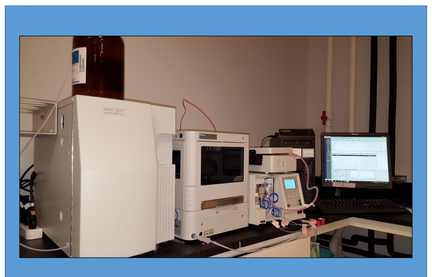

Figure 3. Waters Breeze 2 GPC system

Figure 4. NMR system Bruker AV-III-500HD[2]

Results

- GPC was used to measure the molecular weight (Mol. Wt.) of PLGAs extracted from formulations (Figure 5). These results processed against polystyrene standards for number average/weight average molecular weights.

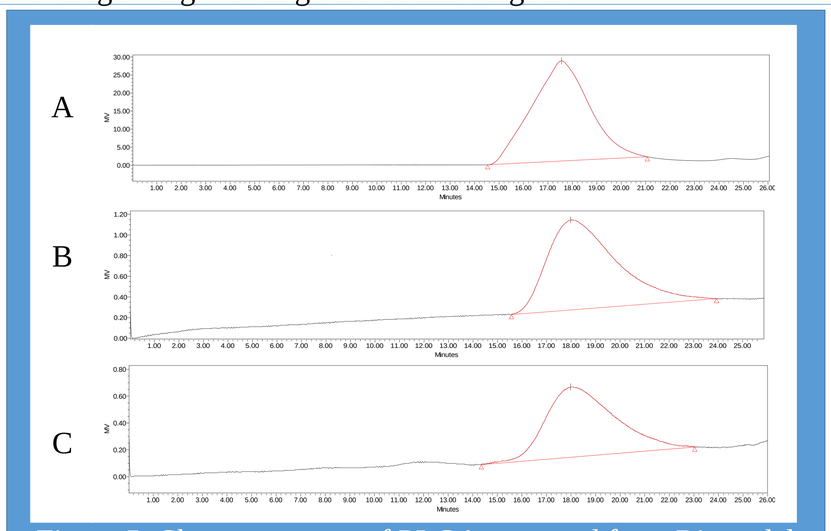

Figure 5. Chromatograms of PLGA extracted from Risperdal Consta (A), Trelstar 11.25 mg (B), and Trelstar 22.5 mg (C).

- Figure 6 shows example HNMR spectra and peak assignments.
- The LA:GA ratio was determined by relative peak integration at 5.2 ppm (LA, 1H) and 4.8 ppm (GA, 2H), respectively.

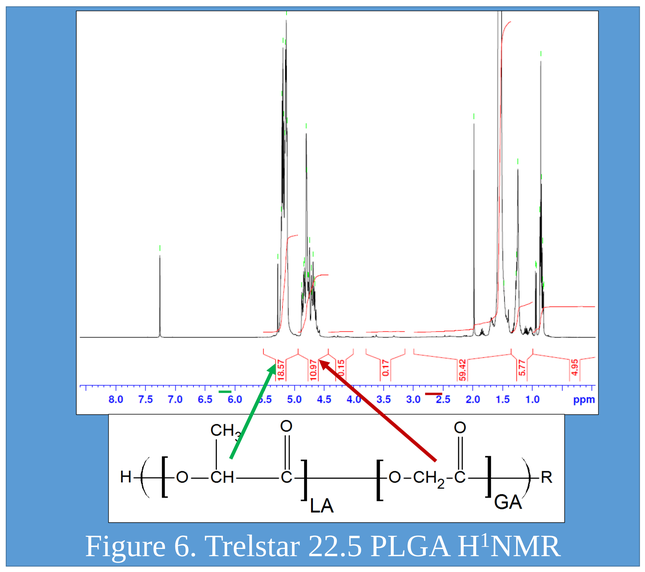

Figure 6. Trelstar 22.5 PLGA H^{1}NMR

- ^{13}C NMR was performed using cryoprobe for a total of 12,000 scans acquired over 12.5 hours to maximize signal/noise ratio.
- Peak at 14 ppm (red arrow in Figure 7) correlates to alkyl endcap carbon and is indicative of ester endcap. Lack of peak indicates acid endcap. All data summarized in **Table 1**.

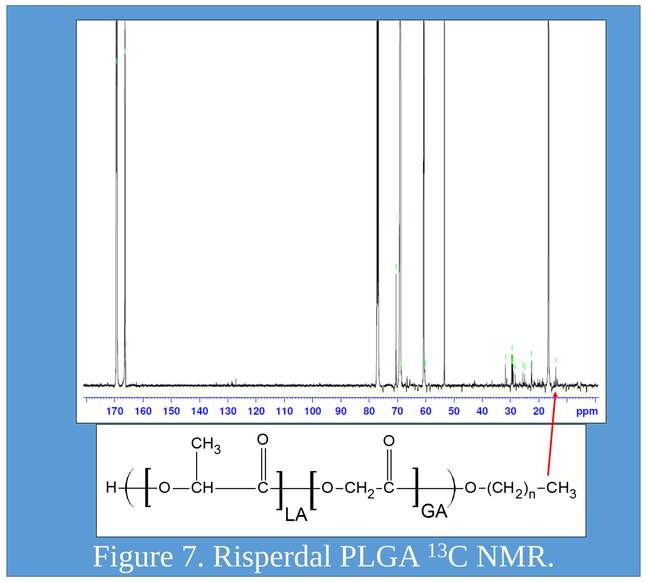

Figure 7. Risperdal PLGA ^{13}C NMR.

Table 1. Formulation PLGA parameters

Product	LA:GA ratio (molar)	Mol. Wt. (Number average)	Mol. Wt. (Weight average)	End cap
Risperdal Consta	78:22	44,875	111,142	Ester
Trelstar (3.75mg)	52:48	25,192	85,207	Ester
Trelstar (11.25mg)	74:26	47,214	72,286	Acid
Trelstar (22.5mg)	77:23	46,368	74,042	N/A

Conclusion

- PLGAs were successfully extracted from formulations for assays of their parameters.
- Using the described method, results indicate that similar PLGAs were used for 3-month and 6-month Trelstar formulations.
  This is unexpected because the two have very different drug release profiles, 3 months vs 6 months.
- One limitation of the current assay method is that **all** PLGAs are extracted, regardless of identity, and assayed together. Thus, the assay presents average properties of different PLGAs rather than properties of individual PLGAs.
- The current method is suitable for formulations containing a single type of PLGA.
- There is a need to develop an advanced assay method which can separate individual PLGAs from a mixture of polymers in a single formulation.

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References:

1. Garner, John, Sarah Skidmore, Haesun Park, Kinam Park, Stephanie Choi, and Yan Wang. "A protocol for assay of poly (lactide-co-glycolide) in clinical products." International journal of pharmaceutics 495, no. 1 (2015): 87-92.
2. http://www.pinmrf.purdue.edu/instruments/av500.shtml

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