Assay of Polymeric Sustained Delivery Systems for Carrier Properties

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PURPOSE

- Establish a testing protocol for characterization of poly(lactide-co-glycolide) (PLGA) used in injectable long-acting depot formulations.
- Allow for examination of the qualitative and quantitative (Q1/Q2) sameness between the reference and generic products.
- Parameters are the molecular weight, lactide:glycolide (L:G) ratio, and endcap group of PLGA polymers.

METHOD

- Commercially purchased Risperdal® Consta®, Trelstar® 3.75, 11.25, and 22.5 mg doses, and Sandostatin LAR® were dissolved in dichloromethane (DCM) (Fig. 1).
- Solutions filtered and dialyzed for three days (MWCO 6000-8000 Da) against an organic solvent.
- Precipitated in a stirring excess of hexane and dried under deep vacuum.
- The polymer component was then analyzed by gel permeation chromatography (GPC) (Fig. 2). ¹H nuclear magnetic resonance (NMR) and ¹³C NMR (Fig. 3). (1)

RESULTS

- GPC chromatographic data used to determine apparent weight average and number average molecular weights (Figure 5). No noticeable differences in the chromatograms were observed for Sandostatin LAR® as compared to other PLGAs.
- The L:G ratio was determined by relative peak integration at 5.2 ppm (LA, 1H) and 4.8 ppm (GA, 2H), respectively (Figure 6 A, B).
- ¹³C NMR was performed using a cryoprobe for a total of 12,000 scans acquired over 12.5 hours to maximize signal/noise ratio. Ester end-capped PLGA could be observed by a peak at 14 ppm in ¹³C NMR. No discrete peaks were observed for glucose (Figure 6 C).
- Table 1 displays parameter values for clinical products assayed.

CONCLUSION

- The molecular properties of PLGAs in three clinical products were determined.
- Trelstar 22.5 mg appears to have similar PLGA as the 11.25 mg, however, it has double the duration (6 months vs 3 months) indicating that this product is likely a combination of two types of PLGA and the assays are revealing the average of the two types.
- According to product labeling, Sandostatin LAR is made of glucose-star PLGA.
- The techniques applied including conventional GPC with refractive index detection, HNMR, and ¹³C NMR do not elucidate any details regarding end-capping, star-structure, or degree of branching.
- There is a need for advanced assay techniques to define parameters of mixed PLGAs and star/branched PLGAs.

ACKNOWLEDGEMENTS AND REFERENCES

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REFERENCES


Table 1. Assayed PLGA parameters of designated clinical products.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>L:G ratio (molar)</th>
<th>M_n (molar)</th>
<th>M_w (molar)</th>
<th>Endcap</th>
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<tbody>
<tr>
<td>Risperdal Consta</td>
<td>78:22</td>
<td>44,875</td>
<td>111,142</td>
<td>Ester</td>
</tr>
<tr>
<td>Trelstar (3.75 mg)</td>
<td>52:48</td>
<td>25,192</td>
<td>85,207</td>
<td>Ester</td>
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<tr>
<td>Trelstar (11.25 mg)</td>
<td>74:26</td>
<td>47,214</td>
<td>72,286</td>
<td>Acid</td>
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<tr>
<td>Trelstar (22.5 mg)</td>
<td>77:23</td>
<td>46,368</td>
<td>74,042</td>
<td>N/A</td>
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<tr>
<td>Sandostatin LAR</td>
<td>58:42</td>
<td>24,549</td>
<td>49,421</td>
<td>N/A</td>
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</tbody>
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