Compositional analysis of glucose-poly(lactide-co-glycolide) in Sandostatin® LAR formulation

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Introduction

The injectable, long-acting formulation of octreotide marketed as Sandostatin® LAR utilizes glucose-initiated poly(lactide-co-glycolide) (Glu-PLGA). A proposed generic product referencing Sandostatin® LAR needs to match the reference listed drug for qualitative and quantitative (Q1/Q2) sameness of Glu-PLGA. The purpose of this study is to utilize nuclear magnetic resonance (NMR) and enzymatic glucose assays to analyze the composition of Glu-PLGA used in Sandostatin® LAR.

Methods

A sample of Sandostatin® LAR (Novartis, 30 mg) was deformulated by dissolution in dichloromethane (DCM), filtration, and reprecipitation in hexane followed by vacuum drying. Samples of the extracted Glu-PLGA were dissolved in chloroform-D (CDCl3) and analyzed by NMR to determine the lactide: glycolide (L:G) ratio [1] and R_c (blockiness) [2]. Separately, the extracted Glu-PLGA was hydrolyzed at 50°C in 0.1 M NaOH followed by drying under vacuum. The obtained residue was analyzed using a colorimetric (based on glucose oxidase) assay to determine the presence of glucose. The resultant material was measured for absorbance at 570 nm by UV-Vis spectrophotometer. A linear PLGA was also hydrolyzed and analyzed as control to confirm specificity of enzymatic glucose assay.

Results

The molar lactide content across 3 samples was determined to be 56.8±1.2% (mean±SD, n = 3) and the R_c value was determined to be 1.46±0.07 (mean±SD, n = 3). The presence of glucose could not be readily confirmed by NMR methods (Figure 1) potentially due to peak overlaps or shielding effects by PLGA. The degraded residues of Glu-PLGA were assayed for the glucose content. The absorbance of the solution at 570 nm was 0.268, and the solution appeared pink, indicating the presence of glucose. The linear PLGA control has an absorbance of 0.123, but appears visually the same as blank as shown in Figure 3. The assay resulted in non-linear response from standard solutions, making it difficult to obtain quantitative data for the glucose content. The method does, however, provide a qualitative assessment for the presence of glucose.

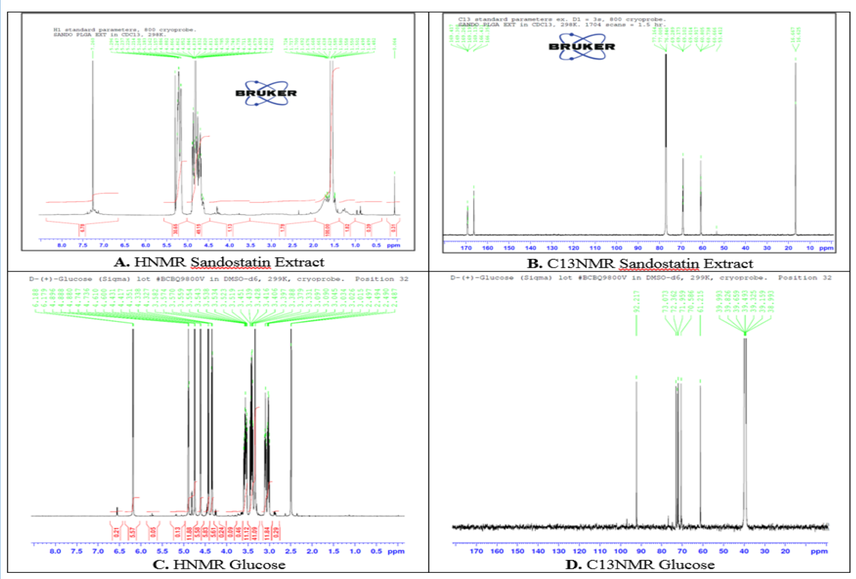

Figure 1. NMR spectra for (A) HNMR and (B) C13NMR for PLGA-Glu extracted from Sandostatin® LAR. For comparison also shown: (C) HNMR Glucose, (D) C13NMR Glucose in DMSO-d6 solvent.

Conclusion

Determination of PLGA properties such as the lactide content and R_c from Glu-PLGA can be accomplished by NMR methods. The presence of glucose was qualitatively confirmed by a colorimetric assay of degraded Glu-PLGA solution. These methods can be used for quality control and establishing Q1/Q2 sameness.

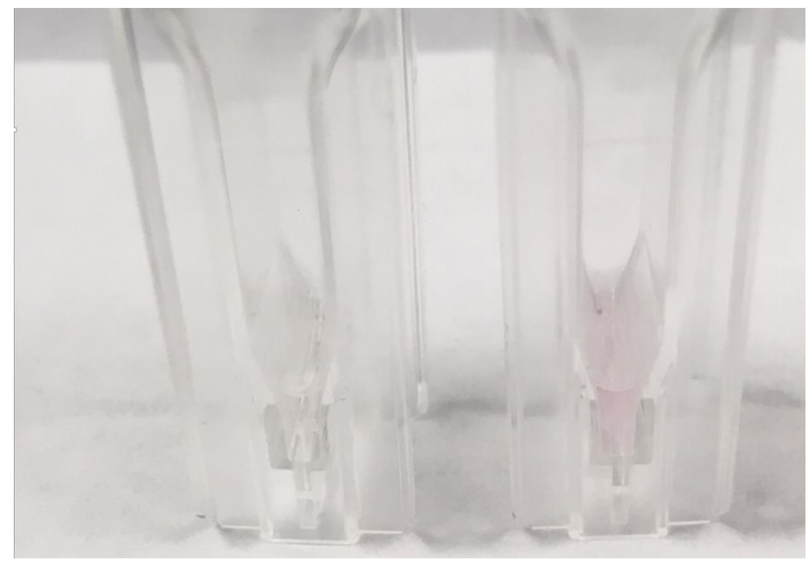

Figure 2. Colorimetric assay results for assay blank (left) and Glu-PLGA extracted from Sandostatin® LAR (right).

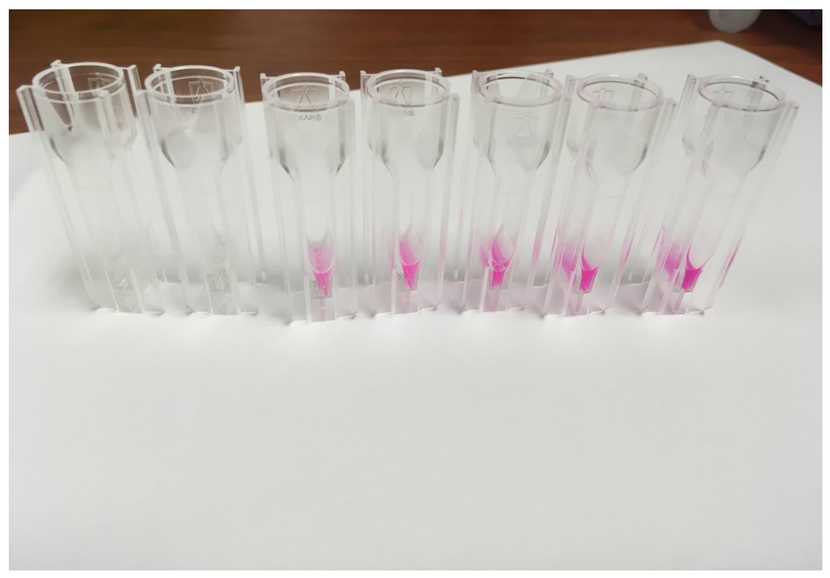

Figure 3. Colorimetric assay from left to right: linear PLGA control, blank, and glucose standards (2 nmol, 4 nmol, 6 nmol, 8 nmol, and 10 nmol).

References

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