Reverse engineering of the one-month Lupron Depot® and development of Q1/Q2 Formulations

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PURPOSE

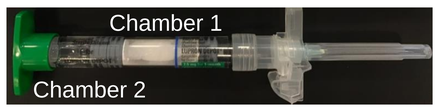
- The 1-month Lupron Depot® (LD) is a poly(lactic-co-glycolic acid) (PLGA) microsphere product which encapsulates and slowly releases leuprolide acetate to reduce injection frequency relative to daily injections of soluble peptide. Despite expiration of patent coverage, there exists no generic for LD on the US market.
- To help enable generic development we sought to:

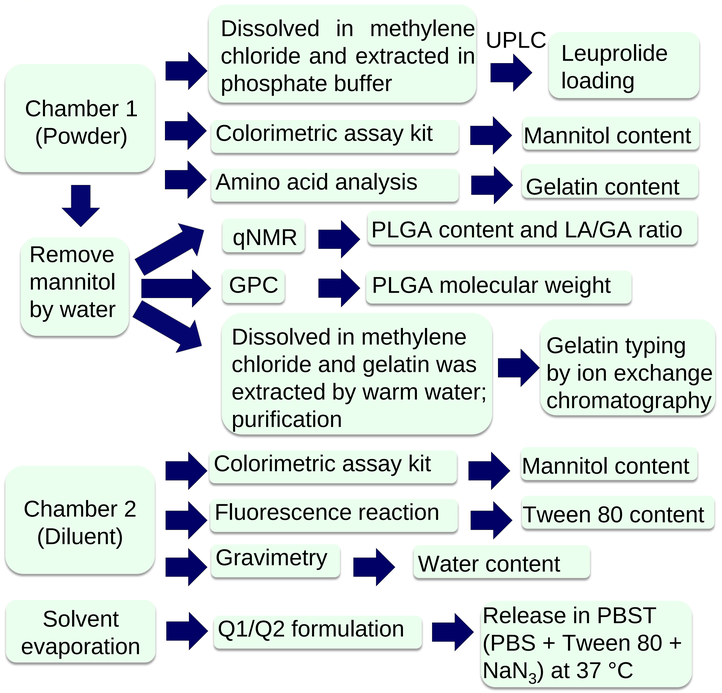
(a) determine the detailed composition of the LD;

(b) develop composition-equivalent microsphere formulation to the LD (Q1/Q2 MS);

(c) assess the drug loading, particle size distribution, morphology and *in vitro* release kinetics of Q1/Q2 MS.

METHODS





RESULTS

- Leuprolide content and several other components in three different batches were determined to be very similar to the literature reported values [1-3] (Figure 1). Preliminary analysis of gelatin content by amino acid analysis indicated 1.52 wt% compared with 1.5 wt% [1].
- Gelatin extracted from the LD displayed a pronounced basic peak as the type B gelatin, indicating that the gelatin used for the LD formulation is type B (Figure 2).
- The 1-month LD has been reported [1-3] to be composed of PLGA with an LA/GA ratio, 75:25; Mw, 12.1 to 14 kDa; and a ratio of Mw to Mn (PDI), 1.6 to 1.7. The PLGA in LD displayed 74.3 ± 0.1/25.7 ± 0.1 LA/GA ratio, 13.04 ± 0.06 kDa for Mw, 8.67 ± 0.05 kDa for Mn, and ~1.5 for PDI which are very close to the previously reported values mentioned above.

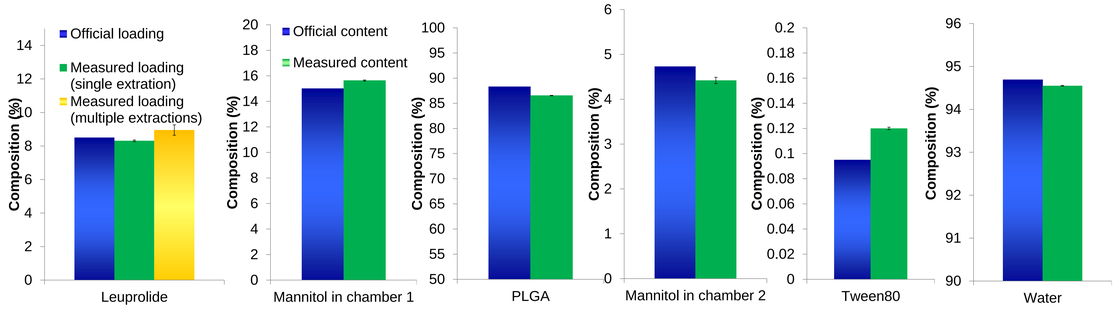


Figure 1. Comparison of official content and measured content of components in chamber 1 and chamber 2 of LD. Columns represent mean ± SEM (n=3).

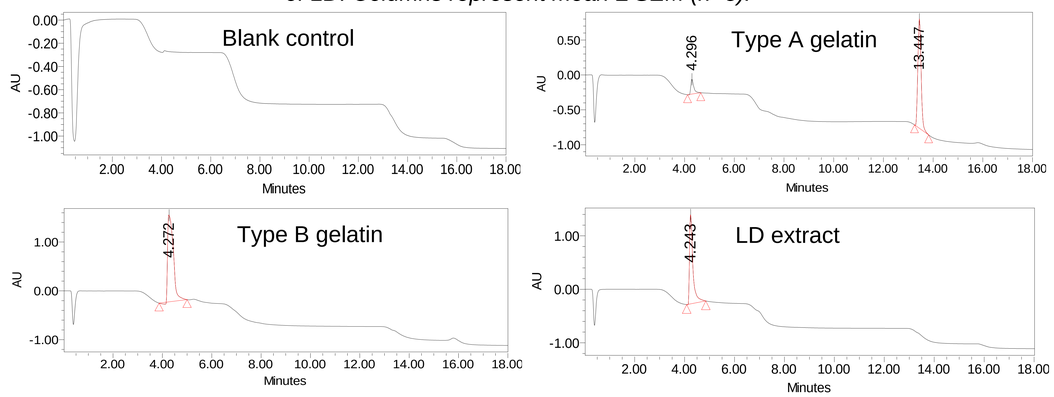
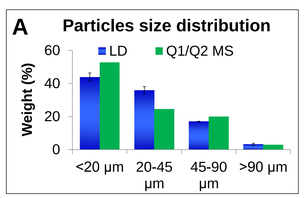
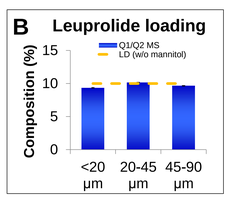


Figure 2. Representative ion exchange chromatograms of blank control, type A gelatin, type B gelatin and gelatin extracted from LD. Pure type A and B gelatins have a major peak at a retention time around 13.5 min and around 4.2 min, respectively. Gelatin used for Lupron Depot formulation was identified as type B.





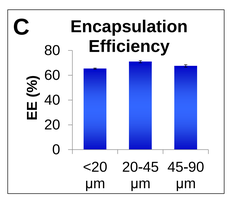
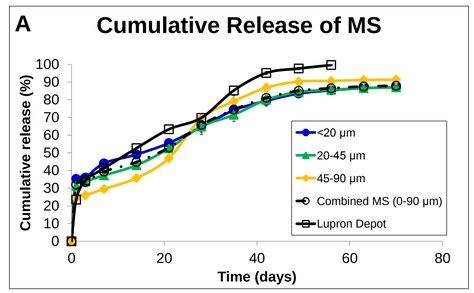
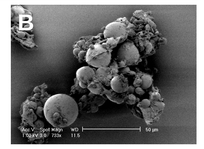


Figure 3. Particle size distribution of Q1/Q2 MS compared to LD (A), leuprolide loading (B) and encapsulation efficiency (C).

- The Q1/Q2 formulation* had desirable loading and encapsulation efficiency of leuprolide, and similar particle size distribution as LD.
- The Q1/Q2 formulation* showed similar long term release kinetics as LD in PBST.

* Note Q1/Q2 designation does not include gelatin analysis.





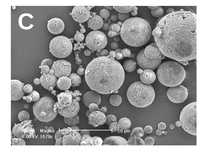


Figure 4. Cumulative release of Q1/Q2 MS as a function of particle size compared to LD (A). SEM images of LD (B) and Q1/Q2 MS (C).

CONCLUSIONS

- Analytical methods for analyzing the specific components of the 1-month Lupron Depot® have been developed and the ingredients have been identified and quantified. The results match well the official content or reported values.
- The Q1/Q2 formulation* described here could be useful for further development of generic leuprolide microspheres, and for assessment of influence of manufacturing process on product attributes and release performance.

FUNDING/ REFERENCE

This research was funded by FDA contract HHSF223201510170C A0001 BAA.

Disclaimer:
This poster reflects the views of the author and should not be construed to represent FDA's views or policies.

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