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Formulation Optimization of PLGA Microspheres Prepared Using a Coacervation Method

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Purpose

Commonly used manufacturing methods for poly (lactic-*co*-glycolic acid) (PLGA) microsphere drug products include solvent evaporation, coacervation (phase separation), and spray drying. Arestin® is a subgingival PLGA microsphere product manufactured by a coacervation method, containing minocycline hydrochloride used to reduce periodontal pocket depth after scaling and root planing. However, it is challenging to evaluate the bioequivalence of such a product due to its complex formulation and local drug delivery. Therefore, it is important to understand the formulation development of minocycline hydrochloride microspheres to facilitate the development of generic equivalents of Arestin® and hence to deliver cost-effective generic product to the public with minimal delay. To achieve PLGA microspheres qualitatively (Q1) and quantitatively (Q2) equivalent to each other, and based on the reference listed drug (RLD), Arestin®, formulation optimization and *in vitro* release profile of minocycline chloride microspheres prepared using a coacervation method was investigated.

Methods

- Briefly, 75 mg of micronized minocycline hydrochloride powder (mean particle size, 3 μm) were dispersed in 3.6 g of a 5% (w/w) PLGA solution in dichloromethane *via* sonication (1 min). The suspensions were added to glass vessels with stirring at 550 rpm, followed by an infusion of 3.6 g polydimethylsiloxane with a viscosity of 350 cSt. The mixture was then discharged into 150 mL of hexane, and stirred at 1300 rpm for 2 hours to solidify the microspheres. The minocycline hydrochloride microspheres were collected by filtration and washed with 100 mL of hexane, followed by vacuum desiccation for 12 hours. The PLGA used was very similar to that used in the RLD (same lactide to glycolide ratio (50:50), same end groups and very close M.Wt.
- The drug loading of the prepared minocycline hydrochloride microspheres and the RLD were determined. Approximately 5 mg of the prepared minocycline hydrochloride microspheres were dissolved in 10 mL of DMSO and analyzed using HPLC.
- The particle size and size distribution of the microspheres were measured by AccuSizer 780A autodiluter particle sizing system (Nicomp, Santa Barbara, CA).
- The *in vitro* release testing was conducted using the sample-and-separate method. Briefly, approximately 4 mg of microspheres were dispersed in 1 mL phosphate buffered saline (containing 0.02 % (v/v) Tween 20, pH 7.4) in 1.5 mL Eppendorf tubes mounted on a rotator set at 100 rpm and incubated at 37 ℃. At predetermined time intervals, the release media were centrifuged, then the supernatants (0.9 mL) were filtered and analyzed by HPLC.

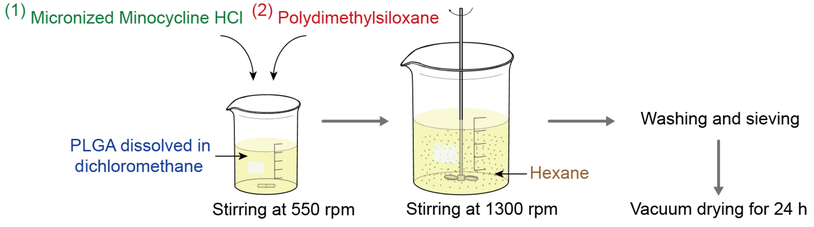

Fig. 1. Schematic of microsphere preparation using a coacervation method.

Results

Table. 1. Drug loading of the prepared minocycline hydrochloride PLGA microspheres with different drug/(drug + PLGA) ratios. The experiments were performed in triplicate (n=3) and the data are presented as mean ± standard deviation.

Formulation	Drug loading (%)
RLD	27.88% ± 0.59%
Formulation 1	29.33% ± 1.05%

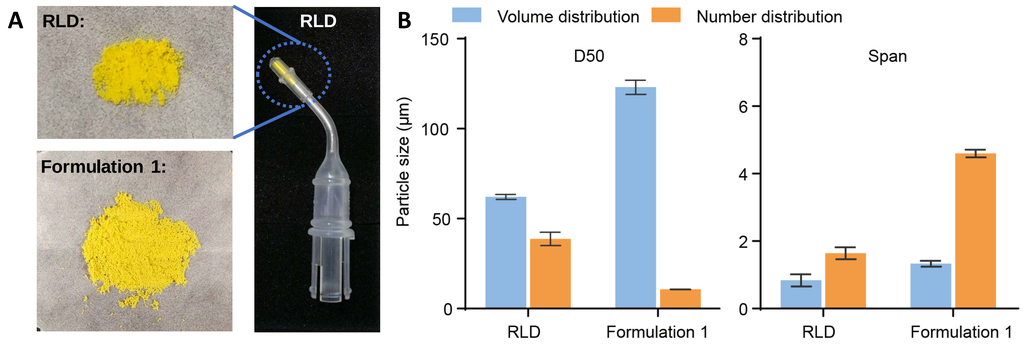

Fig. 2. A) Appearance; and **B)** particle size and size distribution of the RLD and Formulation 1. The experiments were performed in triplicate (n=3) and the data are presented as mean ± standard deviation.

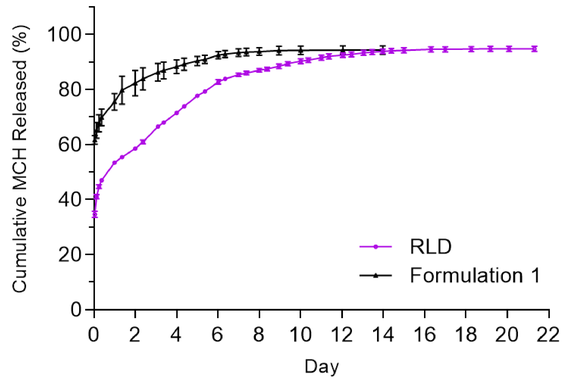

Fig. 3. *In vitro* release profiles of the RLD and Formulation 1. The experiments were performed in triplicate (n=3) and the data are presented as mean ± standard deviation.

Conclusions

- Compositionally equivalent minocycline HCL microspheres of Formulation 1 were prepared using a coacervation method, which had the same appearance as the RLD (Arestin®), as well as a high drug loading of 29.33% that is close to that of the RLD.
- Compared to the RLD, Formulation 1 showed a larger mean particle size and wider size distribution, as well as higher burst release and faster release rate. This may be due to differences in porosity and further research will be conducted to investigate the root cause.

Acknowledgments

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