Application of USP 4 Dissolution Apparatus to Assess Dissolution of Microparticles for Periodontal Disease

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Purpose

Local delivery of antimicrobials has been shown to be advantageous in the treatment of periodontal disease. Arestin® is a microparticle formulation consisting of minocycline hydrochloride, marketed for local application in periodontal disease. Currently, there is no compendial level dissolution method for periodontal microparticles that can differentiate performance of different formulations and demonstrate bioequivalence. In an effort to develop a robust dissolution method, a range of comparators that mimic Arestin® were prepared and their dissolution profiles were determined using a modified USP 4 apparatus. The ultimate goal of this work is to develop a dissolution method that can delineate the effect of processing parameters and formulation changes on product dissolution and can be utilized for quality control and bioequivalence testing of formulations for delivery to the periodontal pocket.

Methods

Acid terminated PLGA microparticles containing minocycline hydrochloride were prepared by a single emulsion method. Using a fractional factorial design, six microparticle products were formulated that varied in the type of organic solvent (ethyl acetate vs. dichloromethane), stirring speed (500, 1000, and 1500 rpm), and PLGA to solvent ratio (0.1, 0.0625, and 0.025). The resulting products were evaluated for size, morphology, and drug content. Dissolution was carried out in a modified USP 4 flow through apparatus under closed loop configuration. In order to separate particles from media, dialysis tubes with cellulose membrane (50 kDa MWCO) were loaded with microparticles dispersed in phosphate buffered saline (PBS). Using 22.6 mm cells that would accommodate dialysis tubes, dissolution studies were performed at 37 °C, 10 mL/min flow rate in PBS. The released drug was analyzed online using a UV-Vis spectrophotometer. Proprietary software, QronoMetrics™ (Qrono Inc.), was used to predict drug release based on the physicochemical properties of the drug, polymer, and particles.

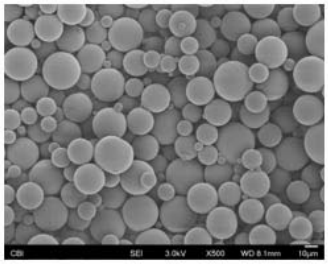
Results

Particles prepared in dichloromethane showed an overall larger particle diameter than those prepared in ethyl acetate as shown by coulter counter measurements. However, SEM imaging indicated both solvents resulted in particles with similar surface morphology. Dissolution performed for 3 days showed complete drug release. Arestin® showed a biphasic release with an initial burst release, a lag phase, and a second burst release (Figure 1B). Comparator products, however, did not exhibit a lag phase. To qualify the application of this dissolution method, proven software for prediction of drug release from PLGA microparticles, QronoMetrics™, was applied. The predicted dissolution differences between Arestin® and a representative comparator product were clearly correlated with the observed dissolution using USP 4 apparatus (Figure 1B).

Conclusion

High similarity was observed between dissolution profiles for minocycline microparticles obtained using a USP 4 apparatus and in silico predictions obtained using the QronoMetrics™ software. Future work will focus on quantitative mechanistic models to predict and validate drug dissolution of periodontal microparticles. Furthermore, this method will be applied to obtain dissolution profiles for bioequivalence studies based on in vitro-in vivo correlations.

A. SEM of a Comparator Product



B. Observed vs. Simulated Dissolution