Title	Development and in-vitro characterization of novel PLGA nanoparticles-Lipid Hybrid (PLH) microparticles for pulmonary delivery of rifampicin
Keywords	Inhalable dry powder, Rifampicin, Polymer-lipid Hybrid
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Abstract	Delivery of anti-tuberculosis drugs directly to the lung as a dry powder formulation based on nanoparticles offers the potential for targeting infected tissues and cells, thereby improving the therapeutic efficacy and reducing systemic toxicity. There is also the capacity for prolonged release and thereby allowing less-frequent dosing. However, deposition of dry powder to the lung is limited due to particle size, i.e. particles >5um tend to deposit in the upper airways and particles < 1um are readily exhaled. Since the direct lung delivery of nanoparticles as a dry powder form is not feasible, the present study aims to design and optimize a novel approach to sustained-release by developing nanoparticle-lipid hybrid (PLH) drug carrier systems composed of PLGA nanoparticles and sub-micron lipid droplets loaded with rifampicin as an anti-TB dosage form and investigate their potential application for lung delivery and to specifically target alveolar macrophages and intracellular bacteria. Rifampicin encapsulated PLH microparticles were successfully synthesized by spray drying of PLGA nanoparticle stabilized lipid emulsions. The resultant dry micron PLH particles were of an ideal size (5.01±1) for dry powder delivery while exhibiting the ability to gradually generated nanoparticles (350 ±50 nm) over time when in contact with the aqueous biological environment. The unique combination of PLGA nanoparticles and submicron lipid droplets aided superior RIF release and macrophage uptake (> 2 fold increment) compared to conventional PLGA micro- and nanoparticles. Thus, the current proof of concept study is an important step towards the development of a hybrid carrier system for pulmonary delivery to improve the treatments of Tb and other infectious lung diseases.

References	1. Andrade, F., et al., Nanotechnology and pulmonary delivery to overcome resistance in infectious diseases. Advanced Drug Delivery Reviews, 2013. 65(13-14): p. 1816-1827. 2. Ohashi, K., et al., One-step preparation of rifampicin/poly(lactic-co-glycolic acid) nanoparticle-containing mannitol microspheres using a four-fluid nozzle spray drier for inhalation therapy of tuberculosis. Journal of Controlled Release, 2009. 135(1): p. 19-24.