Antibiotic-loaded polymeric microspheres for passive lung targeting after intravenous administration

Abstract

Low respiratory tract bacterial infections are currently amongst the leading causes of mortality worldwide. Current treatments consist of oral or intravenous administration of antibiotics. Today’s treatments of pulmonary bacterial infections are often not sufficiently effective due to the difficulty of drugs reaching the infection deep in the lungs, the insufficient drug doses at the site of infection, the development of multi-drug resistance, and the side effects caused by some of the currently used and effective antibiotics. Lung-targeted delivery of antibiotics by using injectable drug-loaded microspheres is a promising alternative to the traditional antibiotic solutions as they achieve local therapeutic concentrations of antibiotics and minimise unwanted off-target effects. This delivery strategy offers potential, especially in the case of patients with compromised lung function or obstruction of the respiratory tract, due to inflammation, infection or significant mucus production, while they still have normal lung perfusion.

The aim of this project was to explore the use of polymeric microspheres as carriers for lung delivery of antibiotics to increase the efficacy of these drugs against bacterial respiratory infections, specifically by selectively targeting the lung capillaries after intravenous administration.

Biodegradable poly(lactic-co-glycolic) acid (PLGA) microspheres encapsulating levofloxacin were prepared with a flow-focusing microfluidic chip and characterized for their physico-chemical properties, and their in vitro and in vivo performance. The PLGA microspheres were highly homogeneous in size with a mean diameter of ~12 μm and coefficient of variation < 5.2%. The microspheres slowly released the encapsulated levofloxacin in a controlled fashion over five days and slightly reduced its antibacterial activity against Pseudomonas aeruginosa, Escherichia coli and Staphylococcus aureus. The microspheres degradation studies showed changes in the internal structure and in the surface morphology, and a faster degradation kinetic in vivo than in vitro. The microspheres showed low toxicity for endothelial and alveolar epithelial cell lines, and did not cause lysis of red blood cells. The biodistribution and pharmacokinetics study showed that 111Indium-labeled microspheres distributed almost exclusively and homogeneously in the lungs after intravenous administration. The microspheres were mostly cleared from the lungs within one week. Overall, intravenous administration of 12 μm PLGA microspheres is suitable for passive lung targeting and is promising for pulmonary therapy.

This project has highlighted the use of microsphere delivery systems as a formulation strategy to target the lungs from the vascular side and deliver amphiphilic antibiotics for the treatment of respiratory infections. The benefits and drawbacks were discussed, and support the use of drug-loaded microspheres to overcome some limitations of current pulmonary treatment strategies.