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Inhalable large porous microspheres of low molecular weight heparin: In vitro and in vivo evaluation

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ABSTRACT

This study tests the feasibility of large porous particles as long-acting carriers for pulmonary delivery of low molecular weight heparin (LMWH). Microspheres were prepared with a biodegradable polymer, poly(lactic-co-glycolic acid) (PLGA), by a double-emulsion–solvent-evaporation technique. The drug entrapment efficiencies of the microspheres were increased by modifying them with three different additives – polyethyleneimine (PEI), Span 60 and stearylamine. The resulting microspheres were evaluated for morphology, size, zeta potential, density, in vitro drug-release properties, cytotoxicity, and for pulmonary absorption in vivo. Scanning electron microscopic examination suggests that the porosity of the particles increased with the increase in aqueous volume fraction. The amount of aqueous volume fraction and the type of core-modifying agent added to the aqueous interior had varying degrees of effect on the size, density and aerodynamic diameter of the particles. When PEI was incorporated in the internal aqueous phase, the entrapment efficiency was increased from 16.22 ± 1.32% to 54.82 ± 2.79%. The amount of drug released in the initial burst phase and the release-rate constant for the core-modified microspheres were greater than those for the plain microspheres. After pulmonary administration, the half-life of the drug from the PEI- and stearylamine-modified microspheres was increased by 5- to 6-fold compared to the drug entrapped in plain microspheres. The viability of Calu-3 cells was not adversely affected when incubated with the microspheres. Overall, the data presented here suggest that the newly developed porous microspheres of LMWH have the potential to be used in a form deliverable by dry-powder inhaler as an alternative to multiple parenteral administrations of LMWH.

1. Introduction

The pulmonary route has recently emerged as a viable alternative to the needle-based route of administration for an expanding array of biotechnology-derived drugs with superior therapeutic activity. However, the vast majority of currently available pulmonary drug delivery systems, including recently approved inhaled insulin—Exubera, which was later withdrawn from the market—are designed as immediate-release formulations to produce local and systemic effects for a short period of time [1]. Little has been done in the development of viable, inhaled formulations of therapeutic agents, especially biopharmaceuticals that can be administered via the lungs to release drugs for a prolonged period. In fact, inhaled long-acting formulations remain elusive because of the lack of efficient delivery devices and optimal drug carriers. The factors that have been major barriers to the development of long-acting pulmonary formulations are (i) suboptimal size and shape of the drug substance or the encapsulating carriers within the respirable fraction, (ii) short residence time of the inhaled drug particles or formulations in the respiratory tract, and (iii) poor loading of drugs into the particulate carriers frequently used to prepare inhaled formulations [2–4].

The recent advances in the dry-powder inhalation (DPI) technology have addressed some of the limitations associated with inhaled formulations, including unwanted loss of drug due to oropharyngeal deposition [5,6]. However, the limitations associated with poor deposition of particles larger than 5 μm have yet to be overcome. In a seminal paper, Edwards et al. first proposed that particles with mass densities <0.4 g/cm^3 and geometric diameter >5 μm could be used to ease respirability as well as to enhance residence time in the lungs [3]. Indeed, the report of Edwards et al. spurred significant growth in studies on PLGA-based large porous particles for delivery of biopharmaceuticals. However, suboptimal pore size of the microspheres and poor encapsulation efficiency of many drugs remain major impediments to the widespread use of large porous PLGA microspheres as carriers for inhaled long-acting formulations [7]. In order to achieve sustained release properties and increase drug load, attempts have been made to modify particulate carriers by using polymer blends [8],

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