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Influence of PEI as a core modifying agent on PLGA microspheres of PGE_1, a pulmonary selective vasodilator

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ABSTRACT

This study tests the hypothesis that large porous poly (lactic-*co*-glycolic acid) (PLGA) microparticles modified with polyethyleneimine (PEI) are viable carriers for pulmonary delivery of prostaglandin E_1 (PGE_1) used in the treatment of pulmonary arterial hypertension (PAH), a pulmonary vascular disorder. The particles were prepared by a double-emulsion solvent evaporation method with PEI-25 kDa in the internal aqueous phase to produce an osmotic pressure gradient. Polyvinyl alcohol (PVA) was used for external coating of the particles. The particles were examined for morphology, size, aerodynamic diameter, surface area, pore volume and *in-vitro* release profiles. Particles with optimal properties for inhalation were tested for *in-vivo* pulmonary absorption, metabolic stability in rat lung homogenates, and acute toxicity in rat bronchoalveolar lavage fluid and respiratory epithelial cells, Calu-3. The micromeritic data indicated that the PEI-modified particles of PGE_1 are optimal for inhalation. Incorporation of PEI in the formulations resulted in an increased entrapment efficiency – $83.26 \pm 3.04\%$ for particles with 1% PVA and $95.48 \pm 0.46\%$ for particles with 2% PVA. The amount of cumulative drug released into the simulated interstitial lung fluid was between $50.8 \pm 0.76\%$ and $55.36 \pm 0.06\%$. A remarkable extension of the circulation half-life up to 6.0–6.5 h was observed when the formulations were administered via the lungs. The metabolic stability and toxicity studies showed that the optimized formulations were stable at physiological conditions and relatively safe to the lungs and respiratory epithelium. Overall, this study demonstrates that large porous inhalable polymeric microparticles can be a feasible option for non-invasive and controlled release of PGE_1 for treatment of PAH.

1. Introduction

The lungs are affected by an array of disorders, including infection, inflammation, obstruction, fibrosis, and vascular diseases such as thrombosis and arterial hypertension. Many lung disorders are currently treated by therapeutic agents that are required to be administered by systemic routes such as the parenteral and oral routes (Ewert et al., 2007; Rubin et al., 2002). Because of this systemic administration, the body is exposed to drugs that may harm other vital organs such as the heart and kidney. Such off-target effects in the treatment of lung diseases can be minimized by administering the drugs directly to the lungs. Indeed, the pharmacotherapy of certain pulmonary disorders, including asthma and pulmonary arterial hypertension (PAH), currently involves the use of nebulizers and inhalers for localized delivery of drugs to the lungs (Olschewski et al., 2002; Papi et al., 2007). However, these formulations or delivery systems suffer from a wide range of limitations that include multiple inhalations a day, short duration of action, metabolic instability in the lungs, and drug loss due to premature deposition in the oropharyngeal tract (Lee and Rubin, 2005; Lipworth, 1995). Short duration of action and metabolic instability often stem from the fact that currently marketed inhalable formulations consist of drug dissolved in a mixture of solvents and propellants or plain drug formulated with respirable lactose (Labiris and Dolovich, 2003). These shortcomings can be addressed in two ways: chemical modification of the drug, or reformulation of the drug in controlled-release polymeric carriers. However, the latter approach is preferred because chemical modification often leads to reduction in pharmacological activity. Chemical modification of heparin, for example, has resulted in reduced anti-coagulant activity (Park et al., 2010).

In fact, polymeric particulate carriers have been used for many years to prolong the duration of action and improve the stability of numerous drugs (Lemoine and Preat, 1998; Shive and Anderson, 1997). Of the various polymeric carriers, poly (lactic-*co*-glycolic acid) (PLGA)-based particles have been extensively investigated for the delivery of drugs via the pulmonary route (Hirota et al., 2010; Ohashi et al., 2009). Moreover, there has been intense interest in

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