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Inhalable PLGA microspheres: Tunable lung retention and systemic exposure via polyethylene glycol modification

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ABSTRACT

Polyethylene glycol (PEG) modification is one of the promising approaches to overcome both mucus and alveolar macrophage uptake barriers in the deep lung for sustained therapy of pulmonary diseases such as asthma. To investigate the feasibility of using PEG-modified microspheres to bypass both barriers, we prepared a collection of polyethylene glycol-distearoyl glycero-phosphoethanolamine (PEG-DSPE)-modified poly (lactide-co-glycolide) (PLGA) microspheres bearing specific PEG molecular weights (0.75, 2, 5, and 10 kDa) and PEG-DSPE/PLGA molar ratios (0.25:1 and 1:1). Drug release, mucus penetration, and macrophage uptake were evaluated *in vitro*, and the corresponding *in vivo* activities of microspheres in rats were investigated. It was found that the PEG_{2000}-DSPE/PLGA 1:1 group showed enhanced mucus permeability and reduced macrophage uptake *in vitro* compared to the PEG_{2000}-DSPE/PLGA 0.25:1 group. At high PEG molar ratios, only the PEG 2000-based group showed significantly prolonged lung retention *in vivo* compared to the control group. The systemic exposure of the PEG_{2000}-DSPE/PLGA 1:1 group was significantly lower than that of the PEG_{2000}-DSPE/PLGA 0.25:1 group (39% of AUC reduction). Additionally, when using the same molar ratio of 1:1, the PEG 2000 group significantly lowered the systemic drug exposure compared to that of the PEG 5000 and 10000 groups (48% and 33% of AUC reduction, respectively), thus making it a promising sustained lung delivery candidate for pulmonary disease treatment.

Statement of significance

Strategies for sustained drug delivery through inhalation have been developed recently, and among these strategies, PEG modification is a promising one. However, it remains unclear whether this approach can be applied to the category of inhalable microparticles to simultaneously overcome both the mucus and macrophage phagocytosis barriers in the lung. In this regard, PEG-modified PLGA microspheres were prepared to investigate their feasibility of achieving these dual functions. The influence of PEG molecular weight and density on *in vitro/in vivo* activities was identified, and the most suitable PEG modification was proved to greatly prolong lung retention and reduce the systemic exposure of drugs; thus, these microspheres could be considered as an underlying sustained lung delivery candidate for pulmonary disease treatment.

1. Introduction

Many pulmonary diseases place heavy burden on health care systems and society, leading to a rapid increase in the fatality rate. Among them, asthma is a chronic inflammatory disease of the conducting airway characterized by reversible airflow obstruction and bronchospasm. Statistics showed that there were 358 million asthmatic patients worldwide in 2015, and the number of patients is expected to rise to 400 million by 2025 [1]. In patient care, inhalation drug products have been widely used for asthma therapy [2]. However, at present, all the commercially available products

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