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Enhanced pulmonary delivery of fluticasone propionate in rodents by mucus-penetrating nanoparticles

Alexey Popov*, Lisa Schopf, James Bourassa, Hongming Chen

Kala Pharmaceuticals, Inc., 100 Beaver Street, Suite 201, Waltham, MA 02453, USA, USA

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ABSTRACT

Most attempts to achieve sustained drug delivery to pulmonary tissues using nanoparticles have focused on mucoadhesive particles (MAP). However, MAP become trapped in the luminal mucus layer and, as a result, are largely eliminated from the respiratory tract by mucociliary escalator and expiratory clearance, which undermines their sustained release potential. Recent studies have shown that mucus-penetrating particles (MPP) engineered to diffuse through mucus can avoid rapid mucociliary clearance *in vivo* and persist in the lung longer. Nonetheless, it has not been confirmed that MPP encapsulating small molecules can sustain drug release in the lung longer than MAP of similar size and core composition. As a proof of concept, we encapsulated fluticasone propionate (FP) into poly(lactide)-based MPP and MAP (both ~200 nm diameter, ~30–35% drug loading) and evaluated their pulmonary residence by measuring FP levels in mouse lungs over 24 h following intratracheal instillation. Furthermore, we evaluated the duration of action of FP MPP in a rat lung inflammation model compared to that of a non-encapsulated FP control. In rodents, pulmonary delivery of FP formulated as MPP provided a 60% higher local exposure compared to MAP and extended the single dose efficacy by at least 16 h compared to non-encapsulated FP.

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1. Introduction

Drug delivery by inhalation is important for treatment of various pulmonary conditions such as allergy, asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and pulmonary infections as it can administer high drug doses rapidly and directly to the site of disease while minimizing systemic exposure and toxicity associated with oral or intravenous dosing (Ibrahim and Garcia-Contreras, 2013; Loira-Pastoriza et al., 2014). Nevertheless, therapeutic efficacy of inhaled drugs is often limited by rapid clearance from the site of action due to absorption into systemic circulation or metabolic degradation in the lungs (Ibrahim and Garcia-Contreras, 2013; Loira-Pastoriza et al., 2014; Olsson et al., 2011), thereby necessitating frequent dosing and increasing systemic liability.

Drug-loaded nanoparticles have been explored as a mechanism to sustain local drug levels in the lungs by virtue of controlled release (Loira-Pastoriza et al., 2014; Mansour et al., 2009; Roy and Vij, 2010; Savla and Minko, 2013). However, many attempts to achieve sustained release from inhaled nanoparticles focused on nanoparticles either purposely modified to be mucoadhesive or mucoadhesive by nature, overlooking the fundamental importance of mucus clearance in the airway as an innate defense against inhaled particles (de Souza Carvalho et al., 2014; Ibrahim and Garcia-Contreras, 2013; Loira-Pastoriza et al., 2014; Olsson et al., 2011; Van der Schans, 2007). The epithelium lining of the tracheobronchial region, upper and central lungs is protected with a layer of mucus gel (2–5 μm in the bronchia, 10–30 μm in the trachea) residing on top of a so-called periciliary layer, 5–55 μm in thickness (Button et al., 2012; Dombu and Betbeder, 2013; Fahy and Dickey, 2010; Savla and Minko, 2013; Van der Schans, 2007). Mucus gel is a complex fluid containing ~95% water, 1–4% proteins and glycoproteins (mucins), with the balance comprising salts, lipids, and various serum and cellular macromolecules. The highly adhesive mesh made by entangled and cross-linked mucin fibers serves to trap airborne pathogens, irritants, and debris, and facilitate their removal out of the lungs by cough and forces of mucociliary beating. While new mucins are continuously synthesized and secreted, these forces transport the luminal mucus blanket at rates of 1–10 mm per min, replacing the luminal gel layer of the respiratory tract every 10–20 min and effectively clearing most entrapped particulates. In contrast, the periciliary layer, which serves to provide a favorable environment for cilia and cell surface lubrication and, according to recent findings, is

* Corresponding author.
E-mail address: alexey.popov@kalarx.com (A. Popov).

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interfused with epithelium-tethered mucins (Button et al., 2012), is cleared much less rapidly. Previous studies have established that microparticles and conventional nanoparticles, even those with diameters as small as approximately 50 nm, are likely to be immobilized in mucus, including respiratory mucus, by adhesive and steric interactions (Kirch et al., 2012a, 2012b; Lai et al., 2009). Upon pulmonary administration, such nanoparticles become trapped in the luminal mucus gel and, as illustrated in Fig. 1, their residence time in the lungs is dictated by mucus clearance (Kirch et al., 2012a; Lai et al., 2009; Loira-Pastoriza et al., 2014; Roy and Vij, 2010). It has been suggested that, to maximize residence time in the lung, nanocarriers must avoid mucoadhesion in the rapidly cleared luminal gel layer and, instead, penetrate readily into the slowly cleared periciliary layer (Lai et al., 2009; Sigurdsson et al., 2013).

Efforts to understand the transport of nanoparticulates through mucus and mucosal surfaces date back several decades (Florence et al., 1995; Jani et al., 1990). While many researches sought to maximize adhesion of particles to mucus in order to improve their retention at mucosal surfaces (Peppas and Huang, 2004), Cone and coworkers showed that viruses and antibodies can diffuse rapidly through human mucus, provided they are smaller than the mucus mesh spacing and have surfaces that do not stick to mucus (Cone, 2009; Olmsted et al., 2001; Saltzman et al., 1994). To overcome the mucus barrier in a similar manner, Hanes et al. introduced the concept of mucus-penetrating particles (MPP), *i.e.* nanoparticles comprised of a polymeric core and having a coating specifically designed to minimize adhesive interactions with mucin fibers (Tang et al., 2009; Wang et al., 2008; Yang et al., 2011; Yu et al., 2012). Using imaging techniques and fluorescently labeled particles, Hanes et al. showed that the ability of the MPP tested to penetrate mucus translated into improved distribution and prolonged particle retention in multiple mucosal organs of animal models (Boylan et al., 2012; Ensign et al., 2012; Maisel et al., 2015; Suk et al., 2014). Specifically, Suk et al. (2014) demonstrated that MPP gene carriers containing compacted DNA and densely coated with poly(ethylene glycol) (PEG) readily penetrated mouse airway mucus *ex situ* and greatly enhanced particle distribution, retention and gene transfer in the mouse lungs compared to similarly sized mucoadhesive nanoparticles. Other groups also produced evidence suggesting that polymeric or liposomal nanoparticles designed with the aim to improve their mucus permeation ability can be promising drug delivery vehicles (Chen et al., 2013; Cu and Saltzman, 2009; Li et al., 2011; Pereira de Sousa et al., 2015). However, to date it has not been confirmed that MPP can prolong retention of a small molecule drug in the lungs, leading to sustained local pharmacokinetics and superior pharmacodynamics or efficacy.

With this manuscript, we sought to address this important missing link and demonstrate the concept of enhanced pulmonary delivery of a small molecule using MPP. For this purpose, we formulated biodegradable polymeric MPP encapsulating fluticasone propionate (FP) as a model drug relevant for pulmonary administration and compared their pharmacokinetics in mouse lung *in vivo* to that of unencapsulated FP nanoparticles and FP encapsulated into mucoadhesive nanoparticles of similar size and core composition. Additionally, we evaluated the pharmacodynamics of FP from MPP in a rat lung inflammation model to confirm that pulmonary delivery of MPP can provide superior efficacy.

2. Materials and methods

2.1. Materials

PLA7A (Polylactide, grade 100DL7A, MW ≈ 108 KDa, intrinsic viscosity 0.7 dL/g) and PLA-PEG (polylactide-*co*-poly(ethylene glycol), grade $100DL_{9K}$-$mPEG_{2K}$) were purchased from Surmodics (Birmingham, AL). Pluronic F127, polysorbate 80, and sodium dodecyl sulfate (SDS) were from Sigma-Aldrich. Fluticasone propionate (FP) with 99% purity was purchased from Beta Pharma, Inc. (Brandford, CT). Flovent® HFA inhaler (Glaxo Group Limited Corporation) was obtained from a local pharmacy by a prescription for R&D use. Nile Red was from Acros Organics. All other chemicals and solvents were from Fisher Scientific unless otherwise specified.

2.2. Test articles for the duration of residence study

Unencapsulated FP nanoparticles (free FP) were prepared by wet milling as described elsewhere (Popov et al., 2015). Briefly, an aqueous dispersion containing 50 mg/mL FP (coarse crystals) and 50 mg/mL SDS was combined in a glass vial with an equal bulk volume of 1-mm ceria-stabilized zirconium oxide beads (Next Advance, Inc., New York). The beads were agitated using a magnetic stirring bar, stirring at approximately 500 rpm, until the target particle size was reached. The obtained fine suspension was diluted with water to a target FP concentration of 1 mg/mL (actual concentration by HPLC: 0.99 mg/mL).

FP-loaded MPP with a covalently attached PEG coating (MPP-PEG) were prepared by nanoprecipitation. A solution containing 10 mg/mL FP, 3.5 mg/mL PLA7A, and 1.5 mg/mL PLA-PEG in acetone was added drop-wise at a rate of 0.5 mL/min to a 40-fold excess of deionized water at stirring. The produced nanodispersion was stirred overnight at room temperature to remove the organic solvent and precipitate unencapsulated drug. The precipitated unencapsulated drug was removed by filtration through a 1 μm glass fiber filter. The nanoparticles were isolated from the filtrate

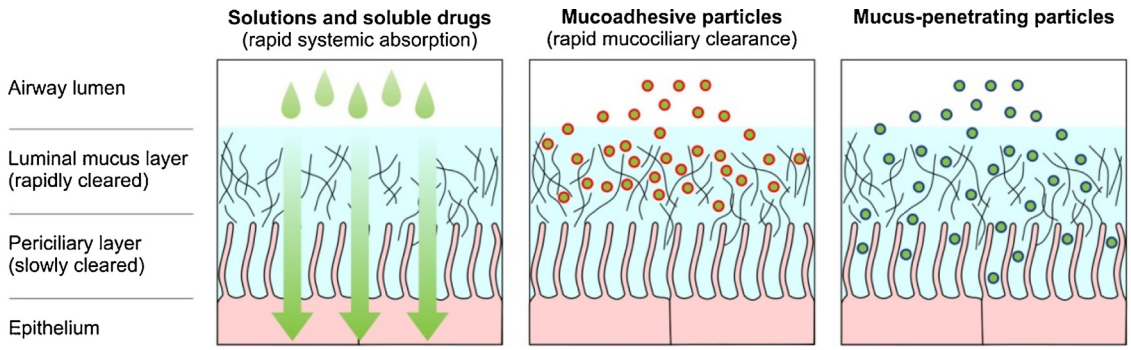

Fig. 1. Depiction of the proposed fate of different formulations upon deposition onto respiratory tissue: solution formulations and soluble drugs are rapidly removed (through absorption) into systemic circulation; mucoadhesive particles are trapped in the luminal mucus gel and eliminated by mucociliary clearance; mucus-penetrating particles avoid adhesion in the rapidly cleared luminal mucus layer and penetrate readily into the slowly cleared periciliary layer.

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