PEG-PLGA Particles of Montelukast and Heparin for Enhanced Anti-inflammatory Effects in Asthma
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Purpose
Montelukast, a cysteinyl leukotriene type 1 receptor antagonist, possesses a series of secondary anti-inflammatory property at a relatively higher concentration. Low molecular weight heparin (LMWH) also exhibits substantial anti-inflammatory effect by interfering leukocyte adhesion and migration. For lung inflammatory disorders such as asthma, combination therapy is preferred over mono-therapy due to its ability to block broad spectrum of inflammatory reactions. Thus, this study tests the hypothesis that an inhalable particle containing montelukast and LMWH is a viable combination therapy for asthma.

Methods
Large porous particles of montelukast and LMWH were prepared using a double-emulsion-solvent evaporation method. Montelukast was first encapsulated in various copolymer based particles using polyethylenimine as a porosigen. The resulting particles were then coated with LMWH. The particles were evaluated for surface morphology, entrapment efficiency, size, density, zeta potential, respirability and release profiles. The anti-inflammatory efficacy of the optimized formulations was studied in ovalbumin sensitized asthmatic Sprague-Dawley rats. The influence of the formulations on bronchoconstriction was measured using a custom-made head-out plethysmograph after methacholine challenge. The infiltration of inflammatory cells was quantified in BAL fluid.

Results
Optimized large porous particles were 10.3 ± 0.7 µm in size and exhibited numerous surface indentations and pores. Formulations showed 66.8 ± 0.4% entrapment efficiency for montelukast with LMWH adsorption efficiency of 91.7 ± 0.8%. Both drugs showed a biphasic release pattern over 4 days. MTT assay revealed minimal cytotoxicity when particles were incubated with bronchial epithelial cells. Similarly, pulmonary administration of particles did not produce significant release of injury markers in BAL fluid. Although asthmatic animals showed >50% reduction in mid-tidal end expiratory flow (EF50), upon treatment with optimized formulation, a 20% reduction in EF50 was observed. Further, infiltrated inflammatory cells in BAL fluid were significantly reduced after particle treatment.

Conclusion
It is feasible to load both montelukast and LMWH in an inhalable particulate system. Proposed novel combinational therapeutic option has potential to generate increased drug concentrations in the lungs and exhibit anti-inflammatory effect for the management of asthma.