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TARGETED PULMONARY SALMETEROL AND FLUTICASONE DELIVERY THROUGH NANO- AND MICRO-MODULATION OF DRUGS AND EXCIPIENTS

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ABSTRACT

Agglomeration/microparticulation of anti-asthmatic/anti-inflammatory salmeterol (SX) and fluticasone (FP) in a single vehicle rendered inefficient pulmonary drug redispersion and site targeting. In the first part of the study, externally drug coated dual-microcarrier against single microcarrier (SX external coat/FP internal coat) systems were designed and examined for their pulmonary drug delivery/targeting profiles. Spray-dried lactose-polyethylene glycol (PEG) 3000 microcarrier were prepared with magnesium stearate lubricant added where applicable. Both single- and dual-microcarrier systems were subjected to cascade impactor analysis against microcarrier particle size and formulation attributes. Small microcarrier (~5 μm) was preferred over larger ones for SX targeting at primary to terminal bronchi. Drug-coated dual-microcarrier enhanced FP inhaled deposition at lower lung due to the absence of external SX barrier and opportunistic hydrophobic aggregation of SX with magnesium stearate-FP deposited on the same microcarrier. Dual-microcarrier increased pulmonary drug retention with a marginal rise in systemic drug levels, and reduced inflammatory lymphocytes/eosinophils/neutrophils infiltration, IL-4/5/9/13 release, mucus production and bronchoconstriction. The second part of the study designed lactose-based microcarrier of nano SX/FP as a function of particle size for tissue targeting and had SX/FP nanoencapsulated by oligochitosan conjugated/complexed with glucuronic acid and intercellular adhesion molecule-1 (anti-ICAM-1) ligands for cell targeting. Conjugate/complex was developed by carbodiimide reaction and coacervation techniques and spray drying method was adopted to produce the solid particles. Lactose-PEG 3000 microparticles (~ 5 μm) and lactose-magnesium stearate microparticles (~ 2 μm) were inclined to deliver nano SX and FP in upper and lower lungs (FPF < 4.5 μm; SX: 45.73 ± 0.52 % and FPF < 3.6 μm; FP: 41.50 ± 0.77 %). Introduction of glucuronic acid and anti-ICAM-1 on nano chitosan of SX/FP raised BEAS-2B cellular uptake of drugs via targeting, membrane permeabilization, and endocytosis (lipid raft and micropinocytosis). These nano oligochitosan-encapsulated drugs profoundly inhibited asthmatic marker (hNF-kβ p65/ERK1/2/p38/JNK/TNF-α/TGF-β/iNOS/COX-2/PGE2/IL-4/IL-5/IL-9/IL-13/IgE) expression in vitro. Rationale micro/nano particle designs increased in vivo pulmonary drug retention in relation to systemic exposure and cAMP promoter of bronchodilation, and reduced expression inflammatory marker (TL1A/PGE2) and Th-2 cytokine (IgE/IL-4/IL-5/IL-13) expression. In conclusion, dual-microcarrier systems (lactose-PEG 3000 microparticles for SX and lactose-magnesium stearate microparticles for FP), nanoencapsulation of drugs with oligochitosan, decoration of nanodrug particles with targeting ligands (glucuronic acid for nano SX and anti-ICAM-1 for FP), and nanoparticles-on-microparticles design are functional strategies to deliver SX and FP by pulmonary route in organ/tissue- and cell-specific manner.

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CHAPTER 1
INTRODUCTION

1.1 Research Background

Asthma is a complex chronic condition characterized by airway obstruction, inflammation, and smooth muscle hyperactivity (Massoth et al., 2019). According to the World Health Organization report, 300 million population is suffered from asthma and this prevalence is projected to increase further by 2050 (Oh et al., 2025; Stewart et al., 2020). Asthma is generally classified into two types: atopic also known as extrinsic asthma (which is stimulated by foreign exposure like dust particles, allergen, pollens, virus, and mold) and non-atopic or internal asthma (gene mutation, respiratory infections, physical activity, stress, drugs, and hormone fluctuation) (Qaid & Long, 2025). Currently, multiple pharmacological treatment options are available to overcome the symptoms which include anti-muscarinic drugs, short acting beta-agonists, leukotriene modifiers, long acting beta-agonists, anti-immunoglobulin modifiers and inhaled corticosteroids (Akram & Wong, 2024). Among these available treatment options, long acting beta-agonists and inhaled corticosteroids are considered the treatment of choice to overcome persistent asthma (Calzetta et al., 2019).

Chitosan, a natural polysaccharide, has gained a significant standing in the field of food, bioengineering, and pharmaceutical industries due to its muco-adhesive, biocompatibility, and biodegradability attributes (Iacob et al., 2021). Baicalein-entrapped chitosan nanoparticles have been synthesized with *in vivo* studies showing a significant capacity to reduce the inflammation in asthma-induced mouse model (Wang et al., 2021). Chitosan-conjugated hyaluronic acid nanoparticles were prepared to deliver heparin for the management of asthma and confocal microscopy analysis showed that the nanoparticles were adequately internalized by the mast cell of rats which translated to an improvement in asthma symptoms (Oyarzun-Ampuero et al., 2009).

With reference to lung diseases such as asthma, pulmonary drug delivery is considered the most convenient approach when compared to oral, parenteral, and transdermal routes (Akram & Wong, 2024). Pulmonary drug delivery avoids first pass effect, exerts direct drug targeting in lungs, reduces systemic drug penetration, and