Dry Powder Aerosols Generated by Standardized Entrainment Tubes From Drug Blends With Lactose Monohydrate: 2. Ipratropium Bromide Monohydrate and Fluticasone Propionate

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ABSTRACT: The objectives of this study were: systematic investigation of dry powder aerosol performance using standardized entrainment tubes (SETs) and lactose-based formulations with two model drugs; mechanistic evaluation of performance data by powder aerosol deaggregation equation (PADE). The drugs (IPB and FP) were prepared in sieved and milled lactose carriers (2% w/w). Aerosol studies were performed using SETs (shear stresses $\tau_s = 0.624$–$13.143\ N/m^2$) by twin-stage liquid impinger, operated at 60 L/min. PADE was applied for formulation screening. Excellent correlation was observed when PADE was adopted correlating FPF to τ_s. Higher τ_s corresponded to higher FPF values followed by a plateau representing invariance of FPF with increasing τ_s. The R^2 values for PADE linear regression were 0.9905–0.9999. Performance described in terms of the maximum FPF (FPF_{max}: 15.0–37.6%) resulted in a rank order of ML-B/IPB > ML-A/IPB > SV-A/IPB > SV-B/IPB > ML-B/FP > ML-A/FP > SV-B/FP > SV-A/FP. The performance of IPB was superior to FP in all formulations. The difference in lactose monohydrate carriers was less pronounced for the FPF in IPB than in FP formulations. The novel PADE offers a robust method for evaluating aerodynamic performance of dry powder formulations within a defined τ_s range. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:3415–3429, 2010

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INTRODUCTION

Successful drug delivery using dry powder inhalers (DPIs) is a challenging task because the forces interacting at the pharmaceutical powder surfaces and the airflow conditions responsible for drug resuspension are complex. The major components and aspects of patient use of DPIs (i.e., formulation, device, and inspiratory maneuver) determine the efficiency and reproducibility of delivering therapeutic aerosols to the desired site of action.

To introduce drug directly into the lungs, the drug particles must be <5 μm in aerodynamic diameter to be respirable. Air–jet milling of the powder is the most commonly used technique for particle size reduction of drugs into the respirable range prior to formulation. The particle size depends on the fluid energy input during the milling of the bulk powder.[1] To overcome the cohesive nature and poor aerosolization of drugs in this size range, and ensure accurate dose metering and manufacturing, respirable drugs are usually mixed with coarse carrier particles, typically α-lactose monohydrate to form an interactive physical mixture. The efficiency of aerosolization of lactose monohydrate-based formulations depends on the interparticulate adhesive/cohesive and resuspension forces which are influenced by a variety of factors, such as drug/carrier particle size,[2,3] particle size distribution,[4]

Additional Supporting Information may be found in the online version of this article.

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morphology,[5] surface roughness,[6] surface energy/crystallinity,[7] ternary components,[8] drug/carrier ratio,[9] hydrophobicity,[10] elastic/plastic deformity,[11] electrostatic behavior,[12] and relative humidity.[13,14] Appropriate particulate interactions allow for a low agglomeration tendency, sufficient ease of flow, and good batch-to-batch variability. These features are required for a good dry powder formulation.

The device is designed to allow efficient drug resuspension through distinct fluidization and deaggregation mechanisms. Currently, there are more than 20 commercial DPI devices in the market and the device design is usually tailored to achieve optimum aerosolization performance of a specific powder formulation.[15,16] However, during the studies intended to focus on formulation effects in performance optimization, the device contribution was often underestimated or simply ignored. The diverse drug aerosolization mechanisms and the incompletely developed airflow conditions of these devices often prevent the comparison of formulation performance results even if the same airflow rate or pressure drop is applied. Consequently, standardized entrainment tubes (SETs) were designed and constructed as device-independent performance evaluation tools that encompass a wide range of specific resistance used in commercial DPIs at defined airflow rate.[17] The SETs have fully developed and well-characterized airflow parameters designated as shear stress (τ_s), Reynolds number (Re), pressure drop (ΔP), and power.[17] The principal deaggregation mechanism of SETs is the turbulent τ_s.[17] SETs allow focus on the formulation, independent of unique device characteristics, in performance evaluation.

In the previous paper in this series, we described the effects of different formulation elements including two drugs (albuterol sulfate and disodium cromoglycate), four lactose monohydrate carriers (milled and sieved), and their corresponding physicochemical properties on *in vitro* formulation performance.[18] The drug aerosolization efficiency was then correlated with SET airflow parameters at an airflow rate ($Q = 60$ L/min).[18] A novel interpretation using powder aerosol deaggregation equation (PADE) was applied to further describe and compare the particulate surface dissociation across a range of τ_s.[18–20] Briefly, PADE is a method that directly correlates SET τ_s with the aerosol performance data (see Eqs. (1) and (2) in the Methods section). It was developed based on the fundamental understanding that the forces acting at the particle interface are analogous to those at the molecular level, and that models of molecular surface association described by an adsorption expression can be adapted to fit shear displacement observations.[20] In principle, drug particles adhere to the carrier surface by fundamental forces including van der Waals, electrostatic, and capillary interactions. As a shear force applies to the surface of a drug-coated carrier particle, drug particles are removed with increasing difficulty because of the sites that they occupy until a saturation is reached, when no drug particle can be removed at increasing shear force unless comminution of particles. The analogy from surface adsorption/desorption leads to a completely novel way of looking at particle interactions. This method is significant because it not only describes the formulation performance across the entire τ_s range, but also more importantly may reveal the mechanism of drug deaggregation during inhalation.[18–20] In order to enhance the fundamental understanding of aerosolization performance from different perspectives (drugs, carrier lactose monohydrate, and SET τ_s) and to further examine the validity of using PADE for formulation performance comparison, two additional drugs intended for delivery to, and with action in the lungs, ipratropium bromide monohydrate (IPB) and fluticasone propionate (FP), were selected to broaden the aerosol formulation performance evaluation, and prediction.

The criteria for drug selection were based on their distinct pharmacological mechanisms of action and physicochemical properties for systematic evaluation of dry powder formulation performance. IPB is a synthetic quaternary *N*-methyl isopropyl derivative of noratropine. As a hydrated salt crystalline powder, it is freely soluble in water and lower alcohol, but insoluble in lipophilic solvents, such as ether, chloroform, and fluorocarbons. It is a highly hydrophilic drug ($\log P = -2.21$).[21] A 1% aqueous solution of IPB has a pH of 5–7.5.[22] IPB induces bronchodilation and inhibits mucus secretion by competitive inhibition of muscarinic cholinergic receptors, causing blockade of acetylcholine-induced stimulation of guanyl cyclase, which, in turn, reduces the formation of cyclic guanosine monophosphate (cGMP), a mediator of bronchoconstriction.[22] It is a nonselective, short-acting bronchodilator (as the approved proprietary aerosol drug product, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) for the treatment of bronchial spasms associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema. It has also been co-administered (as the approved in a proprietary aerosol drug product, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT) with β_2 adrenergic agonist albuterol sulfate through both anticholinergic and sympathomimetic mechanisms, which can achieve additive bronchodilator effect and prevent β_2 agonist-induced bronchospasm.[23]

FP is a synthetic steroid of glucocorticoid family used as an anti-inflammatory agent. FP, a fluorinated corticosteroid ester, is insoluble in aqueous buffer with a pH of 7.4.[24] It is a highly lipophilic drug ($\log P = 3.46$) passing readily through the cell membrane and binding with the corticosteroid receptor.[25] The anti-inflammatory actions of FP in