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Evaluation of Granulated Lactose as a Carrier for Dry Powder Inhaler Formulations 2: Effect of Drugs and Drug Loading

Ping Du [1, 2], Ju Du [1, 2], Hugh D.C. Smyth [1, *]

[1] Division of Pharmaceutics, College of Pharmacy, The University of Texas at Austin, Austin, Texas 78712
[2] Catalent Pharma Solutions, Research Triangle Park, North Carolina 27560

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ABSTRACT

Previously, granulated lactose carriers were shown to improve uniformity and aerosolization of a low-dose model drug. In the present study, the blending uniformity and aerosol dispersion performance were assessed for 2 model drugs salbutamol sulfate (SS) and rifampicin (RIF), blended at high loadings (10% or 30% drug) with granulated lactose carriers. The model drug powders differed in particle size distribution, morphology, density, and surface energies. Content uniformity of RIF blends was better than that of SS. Aerosolization studies showed that all blend formulations had acceptable emitted fractions (>70%). The SS blends showed low induction-port deposition (6%-10%) compared to RIF (5%-30%). This difference was greater at high flow rates. At 90 L/min, the low induction port deposition of SS blends allowed high fine particle fraction (FPF) of 73%-81%, whereas the FPF of the RIF blends was around 43%-45% with higher induction port deposition. However, SS blends exhibited strong flow rate–dependent performance. Increasing the flow rate from 30 L/min to 90 L/min increased SS FPF from approximately 20% to 80%. Conversely, RIF blends were flow rate and drug loading independent. It was concluded that the aerosolization of high drug–loaded dry powder inhaler formulations using granulated lactose, particularly flow rate dependency, varies with active pharmaceutical ingredient properties.

Introduction

Dry powder inhalers (DPI) have become increasingly common in the past decade by virtue of their propellant-free nature, high patient compliance, and improved formulation stability.[1] In DPI formulations, active pharmaceutical ingredient (API) particles need to have aerodynamic diameters around 1-5 μm to reach the target regions of the lung.[2] However, particles with sizes in this range are very cohesive and exhibit extremely poor flowability. In order to facilitate powder flow, metering, dosing, and downstream processing, large mass fractions of coarse "carriers" are commonly introduced to form binary or ternary mixtures.[3] The drug particles attach to the surfaces of the coarse particles, allowing them to be carried from the inhaler device toward the lungs. As the drug-carrier mixtures traverse the inhaler air flow path and flow into the airways, drug particles can detach from the carrier surfaces. Drug liberation occurs on account of flow stream and shear force induced during inhalation,[4] and/or collision or impaction with the inhaler device.[5] Therefore, both high shear force[4] and inertial collision force[5] can foster drug particle liberation and subsequent deep lung deposition. During the inhalation process, carriers eventually deposit in the upper pulmonary system, whereas the detached drug particles continue on to the deeper airways.

To produce a stable and homogenous powder mixture with proper deep lung deposition, a balanced interaction between the drug and carrier particles is required. In the powder blend, the interaction force should be strong enough that the drugs can preferentially adhere to the carrier surfaces resulting in acceptable blend uniformity, yet this interaction must be sufficiently tenuous for detachment of drug particles from carrier.[6,7] Because carriers are the major components of DPI formulations, their properties are critical factors in determining drug delivery efficiency.[8] Research on physical properties of carrier populations has focused on particle size, shape, morphology, surface roughness, surface area, and surface energy.[9-21] Based on results from extensive studies, it is widely believed that carrier particles with smaller diameters (10-75 μm) and fine carrier particles (<5 μm) are preferable to maximize aerosolization efficiency.[12] Small particles have relatively smooth surface. Nevertheless, the small size and smooth surface of particles are detrimental to powder flow[22] and potentially have adverse effects on blending uniformity. In fact, it was reported by Kaialy et al. that budesonide formulated with smaller lactose carriers exhibited higher amounts of budesonide delivered to the lower stages

Data from this research were generated in The University of Texas at Austin, College of Pharmacy, and Division of Pharmaceutics.

* *Correspondence to:* Hugh D.C. Smyth (Telephone: +1-512-471-3383; Fax: +1-512-471-7474).
E-mail address: hugh.smyth@austin.utexas.edu (H.D.C. Smyth).

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of the impactor. These data indicate an improved DPI aerosol performance, while also demonstrating that lactose particles with a smaller diameter had an unfavorable effect on budesonide content homogeneity.[23] Recently, carriers with a large size fraction (>200 μm), especially with significantly rough surfaces, have shown improved aerosol performance.[5,24] This improvement is explained by the switch of the predominant detachment mechanism from turbulence flow to impaction force.[5] Meanwhile, on account of the extremely small cohesive force/weight ratio, these large carrier particles exhibited better flow properties than their smaller counterparts.[5]

The effect of carrier surface properties (e.g., roughness) on drug deposition is complex. A smooth carrier surface with strong adhesive force provides a better drug attachment during mixing, but worse detachment during inhalation. Thus, carriers with smooth surfaces can carry drug particles properly to a patient with a large emitted dose, but may generate a low respirable fraction when compared to carrier with slightly more surface asperities. Nevertheless, the opposite conclusion has also been reported by other researchers; surface roughness can compromise aerosol dispersion.[25-28] The source of contradictory results comes from the different magnitudes of roughness: "micro roughness" and "macro roughness."[29] The micro roughness and macro roughness of carrier particles are differentiated based on the size of drug particles adhered to them. Micro roughness describes a carrier surface when the distance between 2 rough peaks is smaller than the drug particle size. The slight surface asperities increase the interparticulate distances of the drug and carrier particles, leading to weak interparticle interaction and thus a high respirable fraction.[8,25] On the other hand, macro roughness is used to describe a carrier surface if the distance between 2 rough peaks is of the same order as the size of drug particle.[29] An increase in macro roughness multiplies the contact points between the drug particle and the carrier surface.[26] The increase in contact points favors drug adhesion, so in this case, particles with a certain surface roughness do provide better drug content uniformity and stability.[27,28] In spite of a better drug content uniformity, an increase in surface roughness, which increases drug adhesion, also limits drug detachment and compromises aerosol redispersion.[30,31]

The carrier surface property roughness is also relevant to drug loading. Compared to fine drug particles, the lactose carrier is larger and coarser. The large particle size and smooth surface of the carrier particles cause them to have small specific surface areas, which thus limits the loading content of fine drug particles. It was found that when drug loading is increased beyond the amount that would form a monolayer on the available space of the carrier, multiple agglomerate systems are likely to be formed, thereby leading to formulation segregation and reduced aerosol performance.[32,33]

Granulated lactose can be a good candidate drug carrier for dry powder inhalation and high drug loading. A previous study found that significantly larger granulated lactose with super macro roughness improves uniformity and aerosol performance when using a low dose of model drug.[24] Super macro roughness was defined by the distance between 2 rough peaks being 1000 times larger than the size of drug particle. Contrary to macro roughness, the super rough surface of the large granulated lactose carriers actually improved aerosol performance by sheltering more drug particles from press-on forces better than their smooth counterparts.[11,24] A pollen-shaped carrier prepared with hydroxyapatite particles has been proposed as a high drug loading carrier with superior aerosol performance to the lactose carriers with a rocklike shape.[33,34] Previous studies have also reported that porous carrier particles exhibited an improved drug loading compared to smooth particles, during an interactive mixing, without compromising blending uniformity.[35] Although a previous study using granulated lactose investigated only low drug loads (2%), granular lactose is a promising candidate for high drug load on account of its super macro roughness. Additionally, the surface roughness/granule cavity volumes of granulated lactose is positively correlated to granular size.[24] Thus, improved blending uniformity and high drug loading could be achieved using significantly larger granulated lactose (e.g., 200-1000 μm) for DPI formulations.

The other major component of DPIs, the drug particle, also determines the fate of drug delivery from DPIs. There have been many reports studying the aerosol performance of DPI formulations using different drugs. Although coarse, granulated lactose carriers have been proposed as a potential candidate for DPIs with better performance, no studies have been performed to evaluate the effects of drugs with different physicochemical properties on granulated lactose–based DPI formulations. Additionally, it is important to consider a range of doses, especially low and high doses, in DPI. The delivered drug per dose from DPI varies for different medical products. In general, low dose was observed from asthma and chronic obstructive pulmonary disease treatments, whereas relative high dose was required for infection-related diseases. For example, 117 μg of salbutamol sulfate (SS) is delivered from ProAir Respiclick®, whereas around 28 mg of tobramycin is delivered from TOBI Podhaler®. Rifampicin (RIF) is another drug potentially requiring high dose. As an antibiotic, RIF is the first choice drug in the treatment of tuberculosis and the lung is the primary site of infection. Although oral administration of RIF is the current treatment of tuberculosis, pulmonary delivery of high-dose RIF has also been widely studied.[36-38] Therefore, here we investigated the effect of drugs and drug loading of 2 model drugs (SS and RIF) on the performance of significantly large granular lactose (200-1000 μm)–based dry powder formulations. SS was chosen as a model drug and the doses used are not considered for any therapeutic purpose but rather for purposes of evaluating the carrier system with another well-studied inhaled powder. These 2 types of APIs had different sizes, shapes, densities, and surface energies, which was used to evaluate the carrier particle system across a wide range of drug particle characteristics. Follow-up studies where chemistry and size are evaluated in controlled conditions are underway. This study evaluated how different APIs and drug loading strategies affected the aerosol performance over a range of flow rates and the blending uniformity of granulated lactose carrier–based DPI formulations. These studies offer useful insights into the design and optimization of high drug–loaded granulated lactose–based DPI formulations. The effects of different APIs on the aerosol performance underscore the importance of identifying the appropriate physical properties that can help characterize drug deposition profiles. These properties profoundly affect DPI performance in the early stages of formulation development.

Methods

Materials

α-Lactose monohydrate, Pharmatose 100M, was supplied from DFE Pharma (Princeton, NJ). Micronized SS (d50: 1.88 μm) was purchased from LETCO MEDICAL. Deionized water was provided by MilliQ (Millipore). RIF was purchased from Hangzhou Merry Chemical Company (Zhejiang, China). RIF was micronized before use by a lab-scale jet mill (Glen Mills Inc., Clifton, NJ) with a high level (110 psi) of grinding nozzles and a low level (65 psi) of pushing nozzles.

Manufacture of Lactose Granules

Wet granulation was used to manufacture lactose granules with a large diameter using Pharmatose 100M (d10: 63 μm, d50: 150 μm,