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Research Paper

Insights into the roles of carrier microstructure in adhesive/carrier-based dry powder inhalation mixtures: Carrier porosity and fine particle content

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ABSTRACT

To gain insights into complex interactions in carrier-based dry powder inhalation mixtures, we studied the relationships between the carrier microstructural characteristics and performance. We used mercury intrusion porosimetry to measure the microstructural characteristics and to also derive the air permeability of eight carriers. We evaluated the performances of inhalation mixtures of each of these carriers and fluticasone propionate after aerosolization from an Aerolizer®. We did not observe a simple relationship between the carrier total porosity and the performance. Classification of the porosity according to pore size, however, provided interesting insights. The carrier nanoporosity, which refers to pores smaller than micronized drug particles, has a positive influence on the performance. Nanopores reduce the carrier effective contact area and the magnitude of interparticulate adhesion forces in inhalation mixtures. The carrier microporosity, which refers to pores similar in size to drug particles, also has a positive influence on the performance. During mixing, micropores increase the effectiveness of frictional and press-on forces, which are responsible for breaking up of cohesive drug agglomerates and for distribution of drug particles over the carrier surface. On the other hand, the carrier macroporosity, which refers to pores larger than drug particles, apparently has a negative influence on the performance. This influence is likely mediated via the effects of macropores on the powder bed tensile strength and fluidization behavior. The air permeability better represents these effects. The inhalation mixture performance improved as the carrier air permeability decreased. Interestingly, as the carrier fine particle content increased, the carrier microporosity increased and the carrier air permeability decreased. This proposes a new mechanism for the positive effect of fine excipient materials on the performance of carrier-based inhalation mixtures. Fine excipient materials apparently adhere to the surface of coarse carrier particles creating projections and micropores, which increase the effectiveness of mixing. The data also support the mechanism of powder fluidization enforcement by fine excipient materials. The current study clearly demonstrates that the microporosity and the air permeability are key dry powder inhalation carrier performance determinants. Mercury intrusion porosimetry is a useful tool in the dry powder inhalation field; it successfully allowed resolution of carrier pores which contribute differently to the performance.

1. Introduction

Complex interactions in adhesive/carrier-based dry powder inhalation (DPI) mixtures are till date not fully understood. This is mainly underlain by the large number and variety of factors which come into play. The use of analytical techniques that may not quantify these factors to the relevant degree of detail also contributes to the poor understanding. The effects of the carrier surface porosity/roughness on the performance are among the interactions in this domain that are open till date. In carrier-based dry powder inhalation mixtures micronized drug particles with aerodynamic size of 1–5 μm, i.e. respirable, are distributed over coarse carrier particles. Coarse carrier particles improve flow properties of cohesive drug particles.

The carrier surface porosity/roughness influences the aerodynamic performance of carrier-based inhalation mixtures [1–8]. Despite extensive investigations, reported observations are inconsistent and the influence is not yet fully understood. To the best of the current knowledge, the influence of the carrier

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surface porosity/roughness depends on the size of pores/discontinuities in comparison with the size of drug particles [2,9]. Pores and discontinuities larger than drug particles increase the drug-carrying capacity and thus promote drug emission from the inhalation device [2,4]. These large pores, however, provide shelter for drug particle from drag separation forces during aerosolization, thus hinder drug detachment/dispersion from carrier particles, and thus often decrease the drug respirable fraction [2,4]. This negative effect does not apply when dry powder inhalation devices that rely on inertial separation forces are used [8]. It is noteworthy that large pores provide shelter for drug particle also from fictional and press-on forces during mixing; this would have a positive influence on the performance. Prediction of the net effect of large pores is thus not always straightforward. On the other hand, microprojections and pores smaller than drug particles increase the drug respirable fraction, probably by reducing the effective drug-carrier contact area [2,10].

Microscopic studies highlighted the influence of pore size. However, the surface porosity/roughness of dry powder inhalation carriers is most often quantified by air permeametry [1,3,4] and BET gas adsorption [2,5,11], which are in this regard limited. One can derive specific surface areas, but not pore size distributions, from air permeametry measurements. Moreover, specific surface areas derived from air permeametry reflect only large pores and discontinuities. They do not reflect fine and deep pores which do not contribute to air permeability. This explains why several air permeametry studies have suggested carrier surface roughness has a negative impact on the aerodynamic performance [1,3]. This may be indeed true if only large pores and discontinuities are considered. On the other hand, BET gas adsorption provides specific surface areas which include fine pores with diameters down to 0.3 nm. Fine pores may dominate specific surface areas derived from BET gas adsorption. This may explain the outcome of a BET gas adsorption study [7] which suggested carrier surface roughness has a positive impact on the aerodynamic performance. BET gas adsorption provides pore size distributions. Such distributions, however, cover a limited pore diameter range from 0.3 to 300 nm. This range is far below the size range of micronized drug particles used in dry powder inhalation. Pores over this distribution contribute similarly to drug-carrier particle interactions in inhalation mixtures. Such distribution is thus of little value for dry powder inhalation carriers. Laser profilometry [12], image analysis [6], and atomic force microscopy [5,6] have been used for topographic assessment of dry powder inhalation carriers. These techniques are of limited applicability in routine analysis of bulk materials.

The aim of the current study was to gain further insights into the influence of the carrier microstructure on the performance of carrier-based dry powder inhalation mixtures. To this end, we used mercury intrusion porosimetry to study carrier microstructural properties, such as the pore volume distribution and the surface roughness. Mercury intrusion porosimetry allows determination of pore size distributions over a broad pore diameter range from 0.003 to more than 300 μm, i.e. five orders of magnitudes broad. This allows resolution of carrier pores on a scale relevant to the size of micronized drug particles. It is noteworthy that the porosity measured by mercury intrusion porosimetry includes interparticulate spaces and is not limited to surface pores. To our knowledge, the use of mercury intrusion porosimetry for quantification of the porosity of dry powder inhalation carriers has not been earlier considered in the literature. Eight materials, with different chemical nature or crystalline structure, were tested as carriers. These were hydroxypropyl-β-cyclodextrin (CD), dextrose anhydrous (DA), dextrose monohydrate (DM), lactose anhydrous (LA), lactose monohydrate (LM), mannitol (MN), xylitol (XL), and sucrose (SU). These materials are widely available in pharmaceutical quality. The variety allowed us to also test the roles of carrier chemical composition and crystalline/polymorphic form. After processing, the carriers also differed in their contents of fines ($D < 10$ μm), but their coarse components were of almost the same size. Fluticasone propionate, a hydrophobic adhesive drug, was used as model drug. The performances of the inhalation mixtures were assessed after aerosolization from an Aerolizer®. Separation forces generated in an Aerolizer® during inhalation are mainly lift and drag forces.

2. Materials and methods

2.1. Materials

Hydroxypropyl-β-cyclodextrin (Kleptose® HPB), dextrose monohydrate (Roferose® SF; D_{mean} = 50 μm), mannitol (Pearlitol® 50 C; D_{mean} = 50 μm), and xylitol (Xylisorb® 300; D_{mean} = 300 μm) were from Roquette, Lestrem, France. Dextrose anhydrous was from SunTin MediPharma Co. Ltd., Hong Kong, China. Lactose anhydrous (Lactopress® anhydrous 265; β-lactose anhydrous; $D_{50} < 150$ μm; anhydrous lactose is crystallized by rapid drying of a solution of lactose at high temperature; crystals are then milled and sieved to the required particle size distribution) was from Borculo Domo Ingredients, Zwolle, The Netherlands. Lactose monohydrate (Lactohale® LH200, milled α-lactose monohydrate; D_{50} = 50–100 μm) was from Friesland Foods Domo, Zwolle, The Netherlands. Sucrose was from Daqahlia Sugar Co., Cairo, Egypt. Fluticasone propionate (superfine micronized grade; $D_{90} < 10$ μm) was from Jayco Chemical Industries, Maharashtra, India. All other reagents were of analytical grade.

2.2. Preparation of the carriers

We prepared carriers with similar, narrow size-distributions from the carrier original materials by sieving. We sieved each carrier original material through a stack of 150, 106, and 75 μm analytical sieves (Retsch GmbH, Germany) and collected the fraction sieved between the 75 μm and the 106 μm sieves. To minimize the content of fines smaller than 75 μm, we placed the collected fraction below a 75 μm sieve and aerated it for 2 min at 2-bar pressure by Schlick 970 S75 coating gun (Düsen-Schlick GmbH, Germany), placed perpendicularly 5 cm above the sieve. This procedure removes only loose fines. We stored the prepared carriers in polyethylene bags at 20 °C and 45% RH.

2.3. Preparation of the inhalation mixtures

Before mixing, we screened/sieved the carriers and the drug—fluticasone propionate, FP—through a 250 μm sieve to break up and remove agglomerates. We then prepared 1% FP inhalation mixtures (2-g each) in test tubes using the sandwich method. We first vortexed each mixture for one minute. We then added three 4-mm 316 L stainless steel balls to each mixture and vortexed it again for one minute. In order to take the effects of the mixing process on carrier characteristics into consideration, we similarly processed blank carrier samples before further characterization. We stored the inhalation mixtures and the blank carrier samples in polyethylene containers at 20 °C and 45% RH for at least one week to allow for mechanical relaxation.

2.4. Characterization of the carriers

2.4.1. Crystallinity

We measured the crystallinities of the carriers and the drug by differential scanning calorimetry (DSC) using a PerkinElmer DSC 6