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Research Paper

Dry powder inhaler performance of spray dried mannitol with tailored surface morphologies as carrier and salbutamol sulphate

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ABSTRACT

Nowadays, dry powder inhalation as applied in the therapy of pulmonary diseases is known as a very effective route of drug delivery to the lungs. Here, the system of coarse carrier and fine drug particles attached to the carrier surface has successfully been applied to overcome the cohesiveness of small drug particles. Particle properties of both carrier and drug are known to affect drug dispersion as has widely been discussed for lactose monohydrate and various drugs. This study utilises particle-engineered mannitol as an alternative carrier to discover the effect of mannitol carrier particle properties like particle shape, surface roughness, flowability or particle size on aerodynamic performance during inhalation. Spray drying as a technique to accurately control those properties was chosen for the generation of carrier sizes between 50 and 80 μm and different morphologies and therefore various carrier flowabilities. A set of these carriers has then been blended with different spray dried and jet-milled qualities of salbutamol sulphate as model drug to examine the influence of carrier particle properties on aerodynamic behaviour and at the same time to cover the effect of drug particle properties on particle–particle interactions. This experimental setup allowed a general view on how drug and carrier properties affect the Fine Particle Fraction (FPF) as indicator for inhalation performance and gave the first study to distinguish between mannitol carrier particle shape and surface roughness. Further it was possible to relate carrier particle size and shape to drug accumulation and detachment mechanisms during inhalation as size and shape had the main influence on drug detachment. The addition of jet-milled mannitol fines provided an initial insight into the improving effect of ternary powder blends as has been intensively studied for lactose monohydrate but not for mannitol yet.

1. Introduction

Today, local therapy by inhalation is the most common way of active pharmaceutical ingredient (APIs) administration in diseases like asthma or chronical obstructive pulmonary disease (COPD) as it offers dose reduction and a faster onset of action compared to systemic treatment (Hanania, 2008; Maas et al., 2010). An aerodynamic diameter of 1–5 μm is required for the drugs to get entrained to the lower respiratory tract where this so called Fine Particle Fraction (FPF) triggers the therapeutic effect (Daniher and Zhu, 2008; Labiris and Dolovich, 2003).

Dry powder inhalation is the most versatile way of pulmonary administration of API compared to pMDI delivery or nebuliser inhalation. It allows numerous formulation variations and many different dry powder inhaler (DPI) devices to design a drug product exactly matching therapeutic needs. The Novolizer® as a commercially used reservoir inhaler was applied in the present study.

Accurate and reproducible delivery of small API doses (salbutamol sulphate (SBS) as used here: 100–400 μg) is the main challenge in dry powder inhalation (Littringer et al., 2012b). Typically this requires manipulation as dry drug particles are quite cohesive due to their small particle size. Therefore, the system of coarse carrier ($x_{50,3}$ = 50–200 μm) and micronised API particles attached to the carrier surface has been applied to most of the marketed DPIs to improve powder flow and overcome dosing

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concerns (Bechtold-Peters and Luessen, 2007; Boer et al., 2005; Iida et al., 2001). It is clear from literature that particle properties of all components and the nature of the component itself affect DPI performance significantly (Larhrib et al., 2003). Most former studies were dealing with α-lactose monohydrate as carrier to investigate the influences of different particle properties like carrier particle size or morphology on the DPI performance (Iida et al., 2003; Steckel et al., 2006; Zeng et al., 2001; Larhrib et al., 2003; Ming Zeng et al., 2001) using different APIs. At the same time lactose monohydrate is known for drawbacks like partially amorphous spots (Steckel et al., 2006; Vollenbroek et al., 2010), which might cause instability during storage or the fact that it might reduce amine groups (e.g. in peptides or proteins) in a Maillard reaction (Patton and Platz, 1992; Steckel and Bolzen, 2004) because of its reducing character. Thus, mannitol was chosen as alternative carrier material here. This non-reducing sugar alcohol is known to be stable in its β-formation and therefore it can be advantageous regarding storage and application in blends containing proteins or peptides such as used in vaccination formulations.

In general particle–particle interactions between all components of dry powder formulations are based on forces like van der Waals forces or hydrogen bonds that are in turn based on the physicochemical properties of the particle surface. To enable consistent particle surface properties within a batch spray drying was chosen as a technique to prepare mannitol carrier particles of crystalline quality as it is a technique known for maximal control over particle properties (Mescher et al., 2012; Vehring, 2008). Even though most spray dried products emerge to be fully amorphous or with partially amorphous contents (Islam and Langrish, 2010; Müller et al., 2015), mannitol reveals completely crystalline structures after spray drying due to its low glass transition temperature facilitating immediate recrystallisation (Littringer et al., 2012a).

Littringer et al. (2012b) and Mönckedieck et al. (2016, 2017) found that the spray drying process can be used to determine particle properties by process parameters such as atomiser rotation speed, feed concentration or drying temperature. The particles were produced with different particle size and morphology (particle shape and surface roughness) as well as differing porosity and flowability of the bulk.

A defined set of spray dried mannitol carrier particles was blended with spray dried or micronised salbutamol sulphate particles as model API to investigate the influence of these carrier properties on aerodynamic performance. Drug qualities were altered as several studies mentioned drug morphology to impact on detachment of drug particles during inhalation (Larhrib et al., 2003; Zeng et al., 2000). Again, spray drying was chosen to maximise control over API particle properties. Impaction analyses were performed with the Next Generation Impactor (NGI) to obtain the FPF as an indicator for particle–particle interactions affecting drug dispersion.

The aerodynamic performance and accuracy of dosing of such dry powder formulations requires an inhaler device with aligned design to maximise drug dispersion and lung deposition as the interplay of inhaler device and powder formulation are known to significantly influence the inhalation performance. The Novolizer® with its classifier technology (Boer et al., 2006b) was applied for this study as it improves the detachment of the API by centrifugal forces within the device cyclone and impaction forces by small impaction walls (Boer et al., 2006a).

The experimental setup was further extended by the addition of jet-milled mannitol fines as studies performed with ternary powder blends (containing lactose carriers and lactose fines) exhibited improved drug dispersion (Guchardi et al., 2008; Tee et al., 2000; Zeng et al., 1998). The addition of those fines was mainly included to investigate the applicability of theories brought up for lactose based ternary blends to mannitol. In general, fines are thought to be advantageous based on the following theorems: 1. agglomerates consisting of drug and fines tend to be detached easier than single particles (Grasmeijer et al., 2014a; Jones and Price, 2006); 2. fines larger than drug particles serve as a buffer against press-on forces – colliding carriers hit fines but not the drug particles resulting in drugs that are adhered more loosely than without fines (Grasmeijer et al., 2014a; Jones and Price, 2006); 3. fines saturate highly active spots first, so that drug particles get detached easier, when added in the second step (Staniforth, 1996).

The main target of this study was to investigate how particle size, morphology and flowability of spray dried mannitol as alternative carrier affect drug detachment of hydrophilic SBS and thus aerodynamic performance of the DPI formulations. Results are desired to support decisions on best carrier and drug appearance to enable the best performance during inhalation including the addition of a third component like mannitol fines.

2. Materials and methods

Mannitol (Pearlitol® 160C), which was kindly provided by Roquette Frères (Lestrem, France), was used for the spray drying of the carrier particles as well as for the production of mannitol fines. SBS (Selectchemie, Zurich, Switzerland) served as a model API for the aerodynamic characterisation.

2.1. Spray drying of mannitol carriers

Mannitol was spray dried with a non-commercial spray tower in the framework of a Design of Experiments (DoE). The tower was equipped with a laminar operating rotary atomiser (LamRot) where liquid filaments of mannitol (15 % (m/m) dissolved in purified aqua of 25 °C were distributed into the drying chamber through sixty holes at the bottom of the atomiser. This technique enabled the preparation of very narrow droplet size and therefore particle size distributions as shown by Mönckedieck et. al earlier (Mönckedieck et al., 2016, 2017). Particles were prepared using two different inlet temperatures (axial and swirl air stream temperature) and alternating rotary speeds of the LamRot atomiser as factors within a DoE. Three levels were applied for all factors to finally generate nineteen mannitol carrier batches (including five centre points) as followed by a face-centred central composite DoE.

Axial air stream temperatures ranged from 130 to 190 °C, swirl air stream temperatures from 60 to 100 °C, while rotation speeds were varied between 8000 and 14000 rpm. The axial drying air stream entered the tower at the very top facing axially down the tower, whereas the swirl air stream was introduced to tangentially follow the emerging filaments to narrow particle size distributions. All particles were collected at the bottom of the main drying chamber and dried at 100 °C upon the main drying process to avoid moisture. Factors were chosen to generate a broad set of particles exhibiting different particles sizes and morphologies to finally choose six batches to be used in the present study.

2.2. Preparation of salbutamol sulphate particles

SBS particles were prepared by spray drying or jet-milling, respectively, to generate particles of controlled properties regarding size and shape. A commercially available Büchi Mini Spray Dryer B-290 (Büchi Labortechnik AG, Flawil, Switzerland) was used to gain mostly spherical drug particles in three different batches. The spray dryer was equipped with a Ø 2 mm two-fluid nozzle and included a peristaltic pump to ensure continuous feeding. Inlet temperature and mass fraction were altered for the preparation of particles with different properties. SBS SD(S) was prepared with an