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Influence of fine lactose and magnesium stearate on low dose dry powder inhaler formulations

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Abstract

The behaviour of dry powder blends for inhalation, depending on the amount of fine lactose particles smaller than 10 μm and the presence of magnesium stearate (MgSt), was studied in this work. A laser light diffraction method was developed to determine accurately size and volume fraction of these fine lactose particles in coarse carrier lactose ($x_{50} \sim 220$ μm). A linear relationship between measured volume fraction undersize at 10 μm Q_3(10 μm) and added fine lactose could be established. Aerodynamic particle size distribution analysis of lactose showed that the fine lactose was attached to the coarse particles. In the presence of MgSt this interaction was increased. Consequently, the number of free active sites on the carrier surface was reduced and the investigated drug (formoterol fumarate dihydrate) was more effectively delivered. Addition of fine lactose and MgSt improved the aerodynamic performance the drug, as determined by resulting fine particle fraction, by 3% (for each 1% of added fine lactose) and 10%, respectively. Stability tests indicated that added MgSt was the most relevant of the studied parameter to achieve a stable aerodynamic performance. Its ability to protect the moisture uptake into the system was considered as rational for this effect.

Keywords: Formoterol; DPI; Inhalation; Lactose; Magnesium stearate

1. Introduction

Ensuring development and manufacture of effective, reliable and robust drug products is a major objective of pharmaceutical companies. Over recent years it became apparent that inhalation products and specifically dry powder inhaler (DPI) formulations present multiple challenges during development to achieve this goal. A large number of contributing factors to the performance of a DPI system have been studied. However, there is a mutual agreement in the scientific community that parameters closely linked to particle–particle interactions are the main contributors to the behaviour of DPIs as characterised by the aerodynamic particle size distribution (French et al., 1996; Vanbever et al., 1999; Tong et al., 2006).

DPIs commonly consist of a carrier material (alpha-lactose monohydrate), ensuring flowability, reducing agglomeration and providing bulk to make handling and dosing possible, and a relative low amount (0.05–10%) of active pharmaceutical ingredient (API) with particle size typically below 10 μm. Furthermore, some advanced products have been formulated using a ternary agent such as magnesium stearate (MgSt) (Young et al., 2002; Mueller-Walz et al., 2006). However, even this small number of formulation components potentially possesses a wide variability in terms surface characteristics that, in turn, influences parameters such as contact area, and energetic situation on the surface. The energetic situation governs polar and apolar interactions, the influence of humidity, electrostatics and a number of other interactions. Contact area, on the other hand, provides the ground for these interactions to result in forces, acting between particles.

Fine lactose particles in the same size range as the API have been pointed out as key component in this system of forces to improve the formulation performance (Zeng et al., 1998). One of the present hypotheses to explain this phenomenon is based on the presence of active sites and the agglomeration of drug and fine excipient (Jones and Price, 2006). Active sites are interpreted as locations of disturbance on the surface of a crystal were more active molecular groups are presented to the outside. This might be due to simple dislocations in the crystal lattice,

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or the complete distortion of the molecular order. Such regions might have different depth but in every case present areas of higher surface interaction compared with the surrounding crystal areas. The presented paper deals with the influence of fine lactose particles, which can be present in the carrier and resulting in variation in surface and contact area, on the performance of dry powder inhaler formulations. A highly sensitive laser light diffraction method was developed to analyse small variations in the particle size distribution of the carrier. The method was carefully qualified with respect to sample preparation, dispersing conditions and sensitivity.

Although the influence of carriers on the performance of DPI formulations has already been demonstrated in various publications, there is a lack in available literature concerning not only the particle size of the carrier measured by laser light diffraction but also the aerodynamic particle size distribution. The result of these kinds of investigations is likely to be of relevance in gaining better insight into the modelling of the discussed systems. This problem will be addressed in the presented work.

An inhalation product such as a DPI formulation needs to have a stable aerodynamic performance during its designated shelf life to become a commercial product. Moisture has been identified as an important factor for decreasing performance over time (Maggi et al., 1999; Bérard et al., 2002; Price et al., 2002; Young and Price, 2004). It can act as plasticizing agent, changing the surface of the particles and promoting strong adhesion or agglomeration.

Formulations with a low concentration of active substance (such as the formulation studied in this work) are more influenced by the properties of the carrier. This might be associated with the number and availability of active sites on the carrier. In fact, Young et al. (2005) showed that formulations with an active concentration between 0.02 and 0.27% (m/m), deliver about the same fine particle dose (FPD). This observation was explained by the assumption that only after the saturation of active sites a linear increase of the delivered dose with the active concentration is observed (Young and Price, 2006). Therefore, slight variation in present active sides on the carrier (e.g. by changes in manufacturing procedures) might have a significant influence. This work attempts to further elucidate this mechanism.

For this work, the composition of carrier was varied, by changing the amount of fine lactose particles, and by changing the ratio of available surfaces from one carrier substance (lactose) to a controlled mixture of a main carrier and a ternary agent (magnesium stearate). The influence of these changes on the performance of the dry powder inhaler formulation was investigated using a formulation similar to Foradil® Certihaler™ (Novartis Pharma AG CH-Basel, formulation technology and inhaler device developed by SkyePharma AG, CH-Muttenz).

2. Materials and methods

2.1. Materials

Formoterol fumarate dihydrate (formoterol fumarate, FF) was supplied by Novartis Pharma AG (Switzerland), coarse α-lactose monohydrate of pharmaceutical grade (Respitose SV001, $x_{50} = 220\,\mu m$) by DMV International (Veghel, The Netherlands), micronised α-lactose monohydrate ($x_{50} = 5\,\mu m$) by Borculo-Domo (Zwolle, The Netherlands) (also referred to as 'fine lactose' in the following text) and inhalation grade magnesium stearate by Peter Greven (Germany).

Isopropanol, methanol, acetonitrile, glacial acetic acid, perchloric acid were purchased from Merck (Germany) and sodium hydroxide, as 50% solution in water, from Fluka (Switzerland). Deionised water (18 MΩ) was obtained by a MilliQ RG water purification system.

2.2. Blend preparation

Lactose pre-blends containing Respitose and different amounts of fine lactose were prepared as 20 g batches by tumble blending (Turbula mixer, Willy A. Bachofen AG, Switzerland) at 32 rpm for 20 min. The same process was used to obtain lactose–magnesium stearate (0.5%, m/m) pre-blends. Therefore, pre-blends with and without magnesium stearate were mixed following the same procedure. Final blends of FF (0.22%, m/m) with pre-blends were prepared by the same process.

2.3. Laser light diffraction measurements

Laser light diffraction (LLD) analysis was performed using a Sympatec HELOS (Sympatec GmbH, Germany) equipped with a 500 mm lens and a wet dispersion unit (QUIXEL). Pump speed and ultrasonication time, if not further specified, were set at 20% and 60 s, respectively. Isopropanol was used as suspension medium, saturated with lactose and filtered through a 0.1 μm filter. The optical concentration during testing was between 10 and 20%. Data acquisition and calculation was performed by Windox 4 using Fraunhofer theory.

2.4. Aerodynamic particle size distribution

The aerodynamic particle size distribution (APSD) was determined using an eight-stage Andersen Cascade Impactor (ACI) with pre-separator (Copley, UK) operating at an airflow rate of 60 L/min. The impaction plates were coated with a 1% (v/v) solution of Tween 20 (Serva, Germany) in methanol to prevent particle bounce and re-entrainment. The Certihaler (SkyePharma, Switzerland) was used as inhalation device. The powder formulation (560 mg) was filled into the reservoir of the device, which was subsequently assembled with the device body. Ten actuations were discharged at a flow rate of 60 L/min (for 4 s) for each measurement. The amount of FF and lactose deposited in the inhaler, throat, pre-separator, on the individual impactor plates, and stage walls were quantified by HPLC.

The fine particle fraction (FPF) was calculated from the amount of FF with aerodynamic size lower than 4.6 μm divided by total mass recovered. One replicate was performed.

2.5. HPLC analysis of formoterol fumarate

Formoterol fumarate (FF) was analysed by HPLC employing acetic acid (0.5 mol/L) as solvent and a mixture of perchloric