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Characterisation of high dose aerosols from dry powder inhalers

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ABSTRACT

Developments in high dose dry powder aerosol delivery will increasingly challenge the applicability of currently used aerosol characterisation techniques. With cascade impaction analysis bounce effects can negatively influence stage collection efficiency, especially with increasing impactor loads. In this study the suitability of the multi stage liquid impinger (MSLI) and the Next Generation Impactor (NGI) for the characterisation of dry powder aerosols containing up to 50 mg of drug is evaluated. The occurrence of bounce effects is quantitatively assessed by comparison with data obtained from laser diffraction analysis. The liquid based impaction surfaces of the MSLI largely prevent bounce effects, but the low number of cut-off values associated with this impactor hinders accurate data interpretation. With the NGI, a standard high viscosity plate coating insufficiently reduces bounce effects, causing the fraction <1 μm to be higher than what can maximally be expected based on the primary particle size distribution (PSD) obtained from RODOS dispersion. With this type of impactor, the use of solvent soaked filters as impaction surface is necessary to eliminate bounce effects.

1. Introduction

In the field of pulmonary drug delivery advances are made on a regular basis. The administration of highly dosed drugs for an increasing number of therapeutic indications as well as the improvement of already existing therapies is currently investigated in several development programmes. A typical example is the delivery of antibiotics to the lung (Traini and Young, 2009). The higher local drug concentrations along with a lowered risk of systemic side effects associated with the targeted delivery of antibiotics has already proven to be successful in the treatment of cystic fibrosis with tobramycin and colistin. Now also for the treatment of other infectious diseases such as tuberculosis great interest in the pulmonary administration of highly dosed antibiotics exists (Muttil et al., 2009).

Nebulisation is currently the technique used for administration of these high dose antibiotics. However, the well documented drawbacks of this type of treatment have motivated researchers to look for alternatives, with dry powder inhalation being most promising (Hagerman et al., 2006; Labiris and Dolovich, 2003). For a number of antibiotics dry powder formulations have already been developed and new dry powder inhalers (DPIs) capable of effectively dispersing the high antibiotic drug loads have also been reported (Kesser and Geller, 2009; Konstan et al., 2011; Son and McConville, 2011; Traini and Young, 2009). An example is the Twincer™ (de Boer et al., 2006). This high dose dry powder inhaler can disperse up to 50 mg of micronised colistin sulphomethate effectively without excipients. Only a minor amount of lactose sweeper crystals may be desired to minimise inhaler retention. Based on pharmacokinetic data from studies in healthy volunteers and cystic fibrosis patients, such a dose from the Twincer™ is anticipated to be equivalent to the currently used dose of 160 mg from nebulisation (Westerman et al., 2007a,b). The Twincer™, and similar developments in pulmonary drug delivery, will increasingly challenge the applicability of currently used aerosol characterisation techniques for development and registration purposes.

Although the experience in characterising high dose dry powder aerosols containing more than 1 mg of drug is still limited, certain dose dependent artefacts are well known to occur during cascade impaction analysis (CIA). Examples are particle bounce, stage overload and particle re-entrainment, collectively referred to as 'bounce effects'. Bounce effects cause a decrease in the collection efficiency of impactor stages, which results in unreliable and distorted particle size distributions (PSDs). They are described in literature regarding air sampling, and ways to prevent or minimise such bounce effects have also been proposed (Chang et al., 1999; Cheng and Yeh, 1979; Dzubay et al., 1976; Markowski, 1984, 1987; Rao and Whitby, 1978a; Tsai and Cheng, 1995; Turner and Hering, 1987). Examples are the use of a sticky impaction plate coating; altering the impaction surface design; increasing the sampling time and lowering the flow rate through the impactor. The great difference between air sampling and the characterisation of

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inhalation aerosols however, is that the latter is bound to a short sampling time of only a few seconds and strictly controlled air flow rates within the range relevant to inhalation. This range is roughly about a tenfold of the flow rates commonly applied for air sampling, making bounce effects even more likely to occur. As a consequence of these strict conditions, studies on reducing bounce effects during DPI testing have been focused primarily on the use of different materials for coating of the collection plates.

Currently the use of silicone oil and other high viscosity coatings on impactor plates is recommended in both the European and the United States pharmacopoeia when analysing dry powder aerosols (Ph.Eur., 2009; USP, 2007). However, with high dose DPI testing such coatings may not be sufficient to prevent bounce effects once particle saturation of the coating surface has been reached. This subsequently results in particle on particle deposition (Tsai and Cheng, 1995; Turner and Hering, 1987). For example, studies with the Andersen cascade impactor showed that coating of the collection plates alone did not totally eliminate bounce effects when 5 and 10 mg doses of large porous particles were dispersed (Dunbar et al., 2005). It was found that for this purpose a different impaction surface of wetted glass fibre filters is needed. Another study showed that in the Next Generation Impactor (NGI), solvent soaked filters are superior to the normal plate coating in reducing bounce effects when high powder doses are aerosolized and sampled during 20 or 40 s (Rissler et al., 2009). In line with the idea that porous, solvent soaked impaction surfaces are relatively insensitive to bounce effects with increasing dry powder load, the multistage liquid impinger (MSLI) was mentioned as being suitable for the characterisation of 'ultra-high' (cumulative) doses (Wong et al., 2010).

Despite the literature referenced in the previous paragraph on the subject of high dose dry powder aerosol characterisation there are several issues which deserve further investigation. Firstly, some studies have not been performed under the strict conditions as applied during inhalation aerosol characterisation. Secondly, often DPIs are used with poor de-agglomeration reproducibility. This results in large variations of the fine particle fractions (FPFs) generated and therefore, makes it difficult to distinguish between deviations in the PSD caused by the occurrence of bounce effects and those resulting from poor dispersion reproducibility. Furthermore, cumulative doses are sometimes used to reach a high impactor load. PSDs obtained in this manner might be influenced less by bounce effects than those obtained from sampling of a single high powder dose with the same total impactor load, for example due to more time for wetting of particle layers on the coated impaction surface by capillary rise. And lastly, CIA results have never been compared with unbiased aerodynamic PSD profiles of primary particles to support the conclusions regarding the occurrence and minimisation of bounce effects. Therefore, a quantitative assessment of the extent of bounce has never been presented before.

The aim of this study is to take account of all the above mentioned aspects in order to determine which impactor and which type of collection surface is most suitable for high dose dry powder aerosols. For this study the Twincer™ was used, containing up to 50 mg of colistin sulphomethate sodium. With this model drug, the Twincer™ is capable of effectively dispersing all drug loads from 5 to 50 mg in a highly reproducible manner, as shown with laser diffraction technique. Both the NGI and the MSLI were selected for the study as these impactors are widely used and well described in guidelines and Pharmacopoeia. They also contain different impaction surfaces, causing differences in their tendency to show bounce effects. Measurement of the primary drug particle size distribution was performed with laser diffraction technique using the RODOS high-efficacy disperser at high dispersion pressure. This PSD of the primary particles, being unbiased by bounce effects, was recalculated into an aerodynamic size distribution to serve as reference for fine particle fractions obtained in the cascade impactors. Furthermore, in this study impactor tests with solvent soaked filters were performed to investigate whether specially prepared impaction surfaces can prevent bounce effects when sampling high powder weights in a single dose with the NGI under conditions relevant to inhalation aerosol characterisation.

2. Materials and methods

2.1. Formulation and inhaler

The inhaler used is the Twincer™ dry powder inhaler (de Boer et al., 2006). Colistin sulphomethate sodium, micronised with a 50 AS jet mill (Alpine Hosokawa, Germany), was weighed into open aluminium blisters in single doses of 5, 10, 20, 30, 40 and 50 mg. Alpha lactose monohydrate particles in a size fraction of 150–200 μm served as sweeper crystals, keeping the inhaler's classifier walls free from adhering drug particles. For all dose weights approximately 2 mg of the sweeper was added to the blister without mixing with the drug. Sweeper crystals are retained in the classifiers during inhalation and do not disturb the laser diffraction measurements (de Boer et al., 2006).

2.2. Characterisation of the starting material

2.2.1. Laser diffraction analysis

The PSD of the colistin sulphomethate batch was determined in duplicate by LDA based on the Fraunhofer theory using a RODOS dry powder disperser operated at 3 bar and the HELOS BF laser diffractometer (Sympatec, Germany). Dispersion with the RODOS at pressure drops between 0.5 and 5 bar did not result in relevant differences in the particle size distribution, indicating that at 3 bar the PSD of the primary particles is measured. Measurements for the primary particle size distribution were conducted with a 100 mm (R3) lens with a measuring range of 0.9–175 μm.

2.2.2. Helium pycnometry

The density of the powder was measured with a multi helium pycnometer using a small cell (model MVP-1, Quantachrome, USA). The measuring cell was filled with approximately 3 g of the powder.

2.2.3. Scanning electron microscopy

Scanning electron micrographs of the micronised drug were taken using a JEOL 6301F microscope (Jeol, Japan) at an acceleration voltage of 2 kV. Samples were sputter coated with 5 nm of gold/palladium. The micrographs were used for the assessment of a dynamic shape factor of the primary micronised colistimethate sodium particles by comparison with similarly shaped particles having known dynamic shape factors (Hinds, 1982).

2.2.4. Calculations

The mass distribution of the primary particles as function of the aerodynamic diameter was assessed from the volume distribution as function of the laser diffraction diameter, the particle density and the shape factor. This computation, using Eq. (1), was based on class mean diameters which were considered to be equal to equivalent volume diameters, because computations with laser diffraction technique are based on the assumption that particles are spherical. Furthermore, it was assumed that the cumulative volume distribution equals the mass distribution, because solid micronised colistimethate sodium particles have the same density irrespective of their size. There are several uncertainties in this recalculation of the volume distribution from laser diffraction measurement into the mass distribution as function of the aerodynamic diameter