International Journal of Pharmaceutics 478 (2015) 53–59

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

# Extrinsic lactose fines improve dry powder inhaler formulation performance of a cohesive batch of budesonide via agglomerate formation and consequential co-deposition

Hanne Kinnunen [a,*], Gerald Hebbink [b], Harry Peters [b], Deborah Huck [c], Lisa Makein [c], Robert Price [a]

[a] Pharmaceutical Surface Science Research Group, Department of Pharmacy and Pharmacology, University of Bath, BA2 7AY Bath, UK
[b] DFE Pharma, Klever Strasse 187, 47574 Goch, Germany
[c] Malvern Instruments Ltd., Enigma Business Park, Grovewood Road, WR14 1XZ Malvern, UK

ARTICLE INFO

*Article history:*
Received 21 July 2014
Received in revised form 8 November 2014
Accepted 8 November 2014
Available online 13 November 2014

*Keywords:*
Lactose
Dry powder inhaler
Raman spectroscopy

ABSTRACT

The aim of the study was to investigate how the fine particle content of lactose carriers prepared with different types of lactose fines regulates dry powder inhaler (DPI) formulation performance of a cohesive batch of micronised budesonide. Budesonide formulations (0.8 wt%) were prepared with three different lactose carriers (Lactohale (LH) LH100, 20 wt% LH210 in LH100 and 20 wt% LH300 in LH100). Fine particle fraction of emitted dose ($FPF_{ED}$) and mean mass aerodynamic diameter (MMAD) of budesonide was assessed with a Next Generation Impactor (NGI) using a Cyclohaler at 90 l/min. Morphological and chemical characteristics of particles deposited on Stage 2 were determined using a Malvern Morphologi G3-ID. The results indicate that increasing concentration of lactose fines (<4.5 μm) not only increased the $FPF_{ED}$ but also the MMAD of budesonide, suggesting drug deposition in agglomerates. Presence of agglomerates on Stage 2 was confirmed by morphological analysis of particles. Raman analysis of material collected on Stage 2 indicated that the more fine lactose particles were available the more agglomerates of budesonide and lactose were delivered to Stage 2. These results suggest drug-fines agglomerate formation is an important mechanism for how lactose fines improve and regulate DPI formulation performance.

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## 1. Introduction

In dry powder inhaler (DPI) formulations, drug particles with aerodynamic diameters of less than 5 μm are required to target the conducting airways. The particle size is conventionally achieved by secondary processing of crystalline drug using energy intensive air-jet micronisation (Chan, 2006). However, due to the high interparticle forces in micronised, cohesive Geldart type C (Geldart, 1973) powders, and low doses required for drug delivery to the lungs, metering of and fluidising a drug only dose is onerous. Thus, to allow adequate metering and increased flowability of the powder, the micronised drug is commonly formulated with coarser, fluidisable Geldart type A (Geldart, 1973) carrier particles. The carrier of choice for DPI formulations is most often alpha lactose monohydrate.

Historically, a vast number of studies, reviewed by Jones and Price (2006), have shown that the presence of fine lactose particles in a DPI formulation improves the formulation performance in terms of delivered dose. As a general rule, therefore, in addition to the drug and the coarse carrier, fine particle lactose is often present in DPI formulations, either as an extrinsic added fraction of fines or as intrinsic fines within the coarse carrier. However, to date, the exact mechanism for how these fine lactose particles alter the formulation performance has remained unclear, with active sites (El-Sabawi et al., 2006; Ganderton, 1992; Young et al., 2005), drug-lactose fine agglomerate formation (Lucas et al., 1998), and increased cohesion (Shur et al., 2008) theories attempting to explain the phenomenon. Due to the shortcomings of each of these theories, more recently it has also been suggested that all these three theories may be at play simultaneously (Grasmeijer et al., 2014). The concept of total fines, which also takes the concentration of the drug in the formulation into account when defining fines, has also been introduced as an explanation for the improved

* Corresponding author. Current address: School of Medicine, Pharmacy and Health, and Wolfson Research Institute, Durham University, Queen's Campus, Stockton on Tees TS17 6BH, UK. Tel.: +44 191 334 400.
*E-mail address:* hanne.kinnunen@durham.ac.uk (H. Kinnunen).

http://dx.doi.org/10.1016/j.ijpharm.2014.11.019
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performance in the presence of a fine particle component (Thalberg et al., 2012). It has also been suggested that a more favourable powder microstructure for deagglomeration may be achieved by adding lactose fines (Behara et al., 2011).

As required by the regulatory authorities, cascade impactors are routinely used for assessing the DPI formulation performance (European Medicines Agency, 2007). Traditionally, the drug content in the different parts of the impactor is assayed by solution chemistry based techniques. However, some studies have also made an attempt of understanding the mechanisms by which the lactose fines govern the DPI performance by determining the deposition of lactose in the different parts of the impactor alongside the drug determination (Guchardi et al., 2008; Karhu et al., 2000; Srichana et al., 1998b). These studies proved that in addition to the drug, also fine lactose is deposited on the impactor stages. However, due to the limitations of the traditional solution chemistry based analytical techniques, these studies only provided speculative evidence of agglomerate formation between the lactose fines and the drug. Therefore, to study the possible co-deposition of the drug and lactose fines, there remains a need for discovering novel characterisation methods to probe the possible interactions between the lactose fines and drug particles upon deposition.

Combination of the scanning electron microscopy and X-ray microanalysis has been used for studying the interactions between lactose and salbutamol sulphate particles (Srichana et al., 1998a). More recently, Raman spectroscopy has emerged as a promising technique for studying particulate interactions especially in combination pressurised metered dose (pMDI) formulations (Rogueda et al., 2011; Steele et al., 2004; Theophilus et al., 2006). However, also studies where DPI products have been investigated using Raman spectroscopy have been published (Kinnunen et al., 2009; Šašić and Harding, 2010). Both the studies concluded that Raman spectroscopy was a promising technique for studying deposition patterns of DPI formulation components. However, both these studies only demonstrated the capability of Raman spectroscopy in analysing particulate interactions taking place in DPI formulations and were limited in their experimental approach due to low number of particles analysed. Following recent developments in instrumentation, the next step for gaining statistically significant data was taken in the current study as morphologically directed Raman spectroscopy was used for characterising the morphological properties and chemical composition of the material delivered to the impactor stages in parallel with traditional *in vitro* performance assay of the formulations.

The aim of the current study was to investigate the drug deposition in the Next Generation Impactor from DPI formulations containing different amounts and types of extrinsic lactose fines in greater detail using morphologically directed Raman spectroscopy (MDRS) in parallel with *in vitro* performance assessment of the formulations. Particular emphasis of the study was on investigating and quantifying the extent of possible agglomerate formation and co-deposition of lactose fines and a model drug, micronised budesonide, and how this influences the formulation performance as a whole. This was done to enhance the understanding of the mechanisms governing drug delivery from DPI formulations containing fine particle lactose.

## 2. Materials and methods

### 2.1. Materials

Lactohale products, namely a coarse, sieved grade of lactose Lactohale®100, micronised grade Lactohale®300 and a milled grade Lactohale®210 (hereafter designated as LH100, LH300 and LH210, respectively), were all donated by DFE Pharma (Goch, Germany). Micronised budesonide with particle size within the respirable range ($d_{90}$ = 4.40 μm) and a cohesive–adhesive balance (CAB) value of 0.62 (Kinnunen et al., 2014) was received from Sterling S.r.l (Perugia, Italy).

Water used during the study was reverse osmosis purified (Merck Millipore, Darmstadt, Germany). Acetonitrile and methanol were purchased from Sigma–Aldrich (Gillingham, UK) and were of HPLC quality.

### 2.2. Preparation of lactose pre-blends

The fine grades of lactose (LH300 and LH210) were blended with the coarse grade of lactose (LH100) at 20 wt% concentration. Briefly, 20 g of the fine lactose was sandwiched between 80 g of LH100 in two layers in a stainless steel vessel with a volume of 500 $cm^3$. The headspace within the vessel was approximately 1/3 of the volume of the vessel. Turbula (Glen Creston, Middlesex, UK) blending at 46 rpm was applied for 60 min after which the pre-blends were passed through 850 μm aperture sieve to break up any large agglomerates. The pre-blends were stored at 20 ± 2 °C and 44% relative humidity (RH) for at least 24 h before any further work was performed.

### 2.3. Particle sizing of the lactose carriers

The particle size distributions of the lactose carriers were characterised using a Sympatec Helos laser diffraction system equipped with R4 lens and controlled by Windox X software (both from Sympatec, Clausthal-Zellerfield, Germany). The Helos dry dispersion system with the disperser pressure set to 2 bar was used for introducing the powder into the measurement zone in conjunction with Vibri powder feeder with a feed rate of 30% and gap width of 2 mm. The background scattering was recorded for 10 s after which five repeated measurements of 5 s duration were recorded for each of the samples with the optical concentration threshold set to 0.5%. High resolution laser diffraction (HRLD) model of the Windox software was used for converting the raw scattering data into particle size distributions.

### 2.4. Preparation of model DPI formulations

Model DPI formulations were prepared with micronised budesonide at 0.8 wt% concentration in quantities of 40 g. The CAB value of the budesonide (0.62) meant that the drug is adhesive to the lactose and therefore low shear Turbula blending could be used for obtaining a uniform blend between the lactose carrier and the drug particles. Briefly, budesonide was sandwiched between half of the lactose and blended with a Turbula in a stainless steel vessel of 500 $cm^3$ volume for 10 min at 46 rpm. The remaining lactose was then added and further 45 min of blending was applied. The blends were subsequently passed through a 250 μm aperture sieve and stored at 20 ± 2 °C and 44% RH for at least 24 h before any further work was carried out. To ensure that the dose variation was below 6%, the content uniformity of the blends was assessed by taking ten aliquots of 12.5 mg from different parts of the formulation and assaying the drug content within the aliquots.

### 2.5. In vitro *assessment of formulation performance*

Size 3 hydroxypropylmethylcellulose (HPMC) capsules (Qualicaps, Spain) were manually filled with 12.5 mg of the formulations. A Cyclohaler device (Teva Pharmaceuticals, The Netherlands) was used for aerosolising the formulations into a Next Generation Impactor (NGI, Copley Scientific, Nottingham, UK) equipped with a pre-separator. Air was drawn through the impactor at 90 l/min for 2.7 s (Kubavat et al., 2012) as controlled by a TPK critical flow

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