

## Characterisation and Functionality of Anhydrous Inhalation Lactose

C Pitchayajittipong<sup>1\*</sup>, J Shur<sup>1</sup>, J S Kaerger<sup>2</sup>, S Edge<sup>3</sup> & R Price<sup>1</sup>

<sup>1</sup>Pharmaceutical Surface Science Research Group, Department of Pharmacy and Pharmacology, University of Bath, Bath, BA2 7AY, United Kingdom

<sup>2</sup>Aeropharm GmbH, Rudolstadt, Germany

<sup>3</sup>Novartis Pharma AG, Basel, Switzerland

### Summary

A new commercially available inhalation grade lactose was characterised in terms of its physicochemical characteristics and formulation performance and compared to regular inhalation grade lactose monohydrates. The aerosolisation of budesonide from a formulation containing inhalation grade anhydrous lactose was significantly less than formulations employing inhalation grades of lactose monohydrate, ML001 and LH200. Even though there was no apparent relationship between characteristics such as particle size and aerosolisation, there did appear to be a relationship between carrier rheological properties and aerosolisation.

### Introduction

Dry powder inhaler (DPI) formulations typically consist of a homogenous blend, comprising micronised drug particles and a coarse excipient carrier. The carrier, traditionally lactose monohydrate, imparts functionality to the formulation by, for example, improving flow properties and allowing accurate metering. The number of excipients used in marketed DPI is limited, with lactose monohydrate being the excipient of "choice". Non-lactose based excipients, typically carbohydrates, have been used in only a limited number of DPI products and in several DPI development programs, as well as in many academic studies.<sup>1-2</sup> In view of this limited number of regulatory approved excipient carriers, excipient suppliers are increasing their range of products, albeit based on lactose, for use in DPI applications. For example, agglomerated, anhydrous and micronised lactose are now available. However, the relationships between the excipient functionality and DPI performance of such grades have, as yet, to be fully elucidated. Recently, commercially available inhalation grades of anhydrous lactose have been launched. Even though anhydrous lactose is used in a marketed DPI product, the use of any excipient in a DPI development program would require the full characterisation and understanding of the functionality of the excipient, both as a material, and in formulations.<sup>3</sup> This is especially true for inhalation excipients due to the complex nature of DPI products where the performance is, in part, a consequence of surface phenomena.

The aim of the present study was to characterise the physicochemical properties of several different grades of inhalation lactose to further understand the relationships between lactose functionality and DPI formulation performance, with particular emphasis on a new commercial inhalation grade of anhydrous lactose.

### Experimental

Inhalation grade lactose monohydrate (ML001, DMV-Fonterra Excipients, The Netherlands; LH200, Friesland Foods Domo, The Netherlands; Monohydrate 120 M, Sheffield Pharma Ingredients, USA) and inhalation grade anhydrous lactose (Anhydrous 120 MS, Sheffield Pharma Ingredients, USA) were sieved (750 µm) before use. The excipients were characterised using scanning electron microscopy (SEM), dynamic vapour sorption (DVS), X-ray diffraction (XRD), differential scanning calorimetry (DSC), pycnometry, particle size distribution (Sympatec) and powder rheometry. The aerosolisation performance of 200 µg budesonide capsule formulations of each grade of lactose was studied using a Next Generation Impactor (NGI) via a Cyclohaler™ device at 90 L.min<sup>-1</sup>. The aerosolisation characteristics fine particle dose (FPD) (<5 µm) and fine particle fraction (based on loaded dose) (FPF<sub>LD</sub>) were calculated.

### Results

The excipients were characterised in terms of their physicochemical characteristics and their functional performance in a budesonide capsule formulation.

### Physicochemical Characterisation

Typical SEMs of the inhalation grades of anhydrous lactose and lactose monohydrate are shown in Figures 1A and 1B. The physicochemical characteristics of the excipients are shown in Table 1.

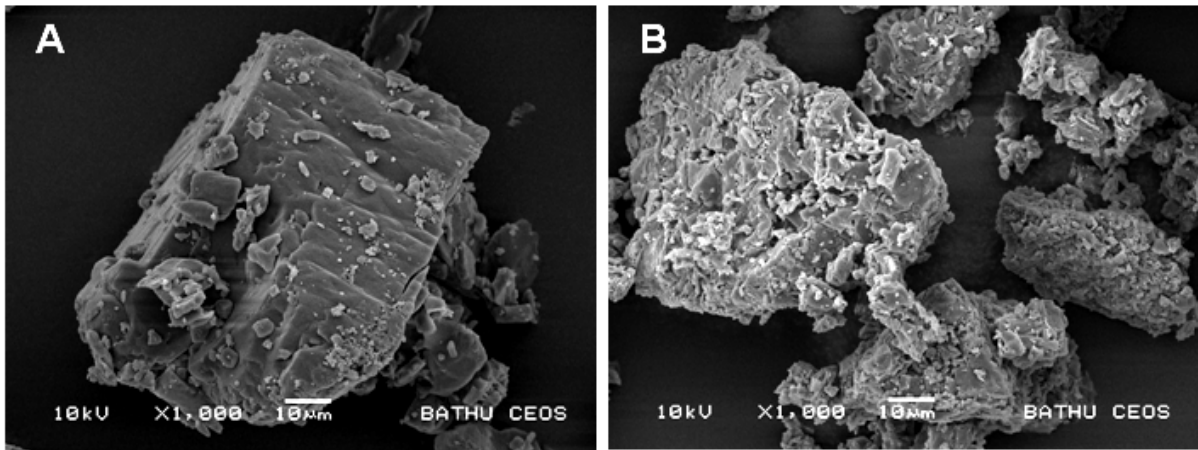


Figure 1. Typical SEM Images of Inhalation Grades of, A: Lactose Monohydrate (LH200) and B: Anhydrous Lactose (Anhydrous 120 MS).

Lactose Grade	Particle Size Analysis ( $\pm$ Std Dev)			True Density g/cm <sup>3</sup> ( $\pm$ Range)	Surface Area m <sup>2</sup> /g ( $\pm$ Range)
	d <sub>10</sub> ( $\mu$ m)	d <sub>50</sub> ( $\mu$ m)	d <sub>90</sub> ( $\mu$ m)		
ML001	2.62 (0.04)	40.66 (0.80)	138.17 (1.11)	1.543 (0.004)	0.88 $\pm$ 0.02
LH200	16.15 (0.32)	85.11 (1.23)	147.22 (1.21)	1.543 (0.004)	0.57 $\pm$ 0.02
Anhydrous 120 MS	7.25 (1.28)	83.54 (1.58)	185.01 (0.94)	1.584 (0.004)	0.43 $\pm$ 0.01
Monohydrate 120 M	11.01 (0.48)	61.01 (0.99)	144.67 (0.99)	1.543 (0.004)	0.82 $\pm$ 0.01

Table 1. Particle Size Distributions, True Densities and Surface Areas of Inhalation Grade Lactose. n=3.

It can be seen from Table 1 that the excipients exhibit a range of particle size distributions and fines content, with ML001 containing the highest level of fines. As expected, inhalation grades of anhydrous lactose and lactose monohydrate exhibited typical physiochemical characteristics.<sup>4,5</sup> For example, the inhalation grade anhydrous lactose exhibits a higher true density than inhalation grade lactose monohydrate. DSC thermograms, (not shown) exhibited endothermic thermal events for lactose monohydrate, at ca. 120-150°C (dehydration) and ca. 205°C (melting) and anhydrous lactose, at ca. 230°C (melting). Powder X-ray diffraction patterns (not shown), were also typical for lactose monohydrate and anhydrous lactose. Typical DVS data for inhalation grades of lactose monohydrate and anhydrous lactose is shown in Figure 2. As expected, anhydrous lactose absorbs relatively more water at higher water activity than lactose monohydrate. Upon de-sorption, the apparent increase in mass of the anhydrous lactose is due to the presence of lactose monohydrate. Both materials exhibit relatively low moisture sorption at relative humidities less than 70%.

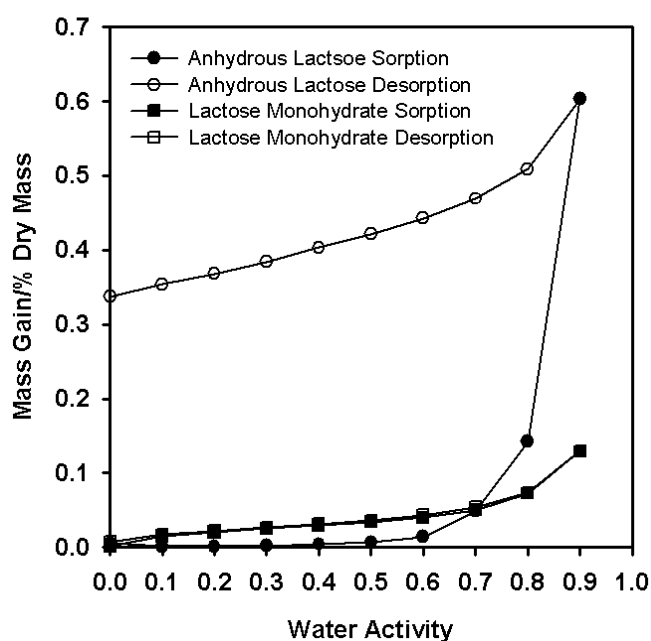


Figure 2. Typical DVS Absorption and Desorption Profiles of Inhalation Grades of Lactose Monohydrate (LH200) and Anhydrous Lactose (Anhydrous 120 MS).

The different grades of lactose were characterised using a FT4 Powder Rheometer (Freeman Technologies, Welland, UK) to determine the energy required to fully fluidise the different powders. In each case, 20 ml of sample powder was analysed in a 25 mm bore cylinder. The samples were conditioned using a 23.5 mm blade which was moved down a helical path with a helix angle of 5 degrees at 20 mm/s. Rheological studies ( $n=3$ ,  $\pm$  Std Dev) suggested that the excipient carriers exhibited fluidisation energies of  $24.0 \pm 2.9$  mJ,  $19.9 \pm 1.1$  mJ,  $10.3 \pm 1.8$  mJ and  $11.9 \pm 1.4$  mJ for ML001, LH200, Monohydrate 120MS and Anhydrous 120MS, respectively.

### Pharmaceutical Functionality

In order to investigate the possibility of using inhalation grade anhydrous lactose in carrier based formulations, a 200  $\mu\text{g}$  dose blend of budesonide was prepared using each of the 4 lactose grades. The blend, after confirming acceptable blend uniformity, was added (25 mg) to size 3 HPMC capsules and aerosolised into a NGI at 90  $\text{L}\cdot\text{min}^{-1}$  using a Cyclohaler<sup>TM</sup>. The fine particle dose (FPD) of budesonide varied between 20 - 50  $\mu\text{g}$ , depending on the grade of lactose employed in the formulation (Table 2).

Grade of Lactose	Emitted Dose ( $\mu\text{g} \pm \text{S.D.}$ )	FPD ( $\mu\text{g} \pm \text{S.D.}$ )	FPF <sub>LD</sub> ( $\% \pm \text{S.D.}$ )
ML001	173.5 (7.9)	49.2 (4.9)	26.0 (1.7)
LH200	188.5 (2.6)	35.2 (1.6)	17.7 (0.6)
Anhydrous 120 MS	185.2 (2.7)	24.8 (1.3)	12.7 (0.7)
Monohydrate 120 M	174.1 (3.5)	24.7 (1.7)	13.1 (0.9)

Table 2. Aerosolisation Performance of Budesonide (200  $\mu\text{g}$ ) using Lactose Carriers. ( $n=3$ ).

These data suggest that there was no relationship between lactose characteristics, such as particle size and powder density, and *in-vitro* performance. However, and interestingly, powder rheology studies suggested that there was a relationship between fluidisation energy and fine particle dose with an improved aerosolisation being observed with increasing fluidization energy (Figure 3). These data are supported by a previous study which reported that materials with high fluidisation energies possess greater tensile strength, which shifts the minimum fluidisation velocity, resulting in the generation of higher aerodynamic drag forces within a DPI device that may result in increased liberation of fine drug particles as observed in this study.<sup>6</sup>

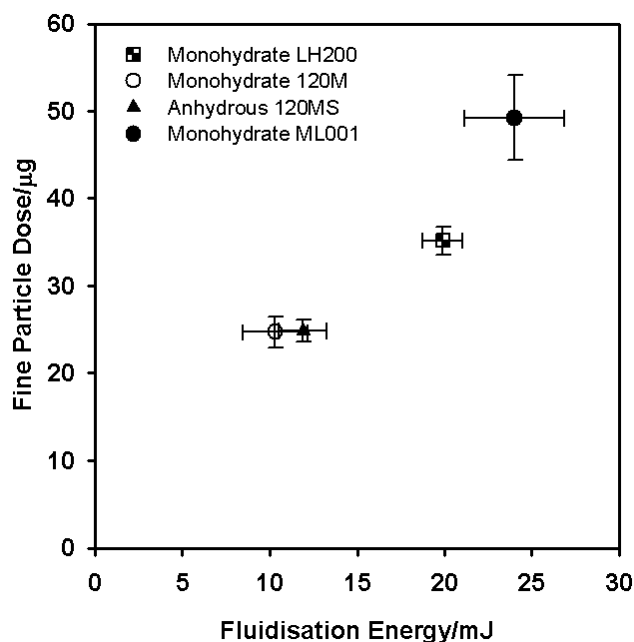


Figure 3. Relationship Between Aerosolisation Behaviour and Fluidisation for Various Grades of Inhalation lactose.

### Discussions and Conclusions

In conclusion, a new commercial inhalation grade of anhydrous lactose was fully characterised in terms of its physicochemical and powder properties and compared to regular inhalation grades of lactose monohydrate. No correlation between such material characteristics and DPI performance has, at present, been identified. However, the fluidisation behaviour of different inhalation grades of lactose could be related to DPI performance. These data suggest that inhalation grades of anhydrous lactose can be readily characterised and, importantly, the rheological fluidization properties of lactose powders may provide important functional information regarding carrier-based excipients.

### References

1. H. Steckel, N. Bolzen. (2004). Alternative sugars as potential carriers for dry powder inhalations. *Int. J. Pharm.*, 270, 297-306.
2. S. K. Tee, C. Marriott, X. M. Zeng, G. P. Martin. (2000). The use of different sugars as fine and coarse carriers for aerosolised salbutamol sulphate. *Int. J. Pharm.*, 208, 111-123.
3. S. Edge, S. Mueller, J. Shur, R. Price. (2008). Factors affecting defining the quality and functionality of excipients used in the manufacture of dry powder inhaler products. *Drug Dev. Ind. Pharm.*, 34, 966-973.
4. J. H. Kirk, S. E. Danna, C. G. Blatchford. (2007). Lactose: A definitive guide to polymorph determination. *Int. J. Pharm.*, 334, 103-107.
5. C. F. Lerk, A. C. Andreae, A. H. de Boer, P. de Hoog, K. Kussendrager, J. van Leverinke. (1984). Alterations of  $\alpha$ -lactose during differential scanning calorimetry. *J. Pharm. Sci.*, 73, 856-857.
6. J. Shur, H. Harris, M. D. Jones, J. S. Kaerger, R. Price. (2008). The role of fines in the modification of the fluidization and dispersion mechanism within dry powder inhaler formulations. *Pharm. Res.*, 25, 1631-1640.