Engineered Carrier with a Long Time of Flight (TOF) to Improve Drug Delivery From Dry Powder Inhalation Aerosols.

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Summary
A lactose carrier with long TOF was engineered to improve drug deposition from DPIs. The particles were engineered by contacting spray-dried particles with a solvent in which these have a poor solubility. The process increased the particles hollow volume without affecting their original shape. The long TOF was demonstrated by carrier deposition in the lower stage of the TSI, which was up to 9-fold higher compared to the conventional lactose. The highest deposition of the long TOF carrier was obtained at the lowest inhalation flow rate (24 L/min). The % Fine Particle Fraction of salbutamol sulphate was up to 50% when long TOF carrier was used. Importantly, this study has shown that adhesion drug/carrier has no negative effect on drug deposition, when a long TOF carrier is used.

Introduction
Despite recent advances in drug particle engineering approaches, micronisation or fluid energy/jet milling remain the processes of choice in inhalation product development, owing to their simplicity, established scale up and conformity to existing manufacturing and development operations (Schiavone et al., 2004). However, these particle formation methodologies suffer from many drawbacks resulting in poor product performance. Thus, improving drug delivery efficiency from dry powder inhalation aerosols (DPIs) using micronised drug is still a challenge. Large carrier particles, such as lactose, are usually mixed with micronised drug particles to reduce cohesion between the primary drug particles and improve formulation flowability, thus improving dosing accuracy and minimizing the dose variability observed with drug formulations (Timsina et al., 1994). It also follows that, since the drug is always mixed with a carrier and the carrier is present at a much higher concentration than the drug in the formulation, improvements in the properties of the carrier should also improve drug deposition. In general, the morphology and roughness of carrier particles are not uniform. These differences in carrier morphology and roughness may lead to differences in apparent adhesion properties of drug particles (Young et al., 2005). The strong adhesion of drug particles to the carrier during aerosolisation could result in a highly variable dosing and poor aerosol performance. The retention of drug particles on the carrier may be inconsequential with drugs that are not very potent and have large therapeutic indices, with potent drugs, it is very critical to control the doses. Despite enormous efforts made to lower the adhesion between drug and carrier to promote drug detachment, the coarse carrier used in most of the cases has a short time of flight in the air-stream caused by its large size (≥63μm) and density. Therefore, the carrier will impact rapidly whilst most of drug particles still adhere to its surface. All carriers used for DPIs to date are not appropriate to deliver drugs with a high adhesion and sticking tendency to the carrier. Increasing the carrier time of flight will allow more time for drug detachment. The detached air-borne drug particles may undergo further deaggregation during flight time in the airways to produce a particle size suitable for deep lung penetration. Any proportion of drug remaining adhered to the carrier is likely to travel further to reach deep the lung. The aim of this work was to engineer spherical lactose carrier particles having a long time of flight and to examine the deposition profiles at different flow rates of lactose and salbutamol sulphate from formulations employing conventional lactose and engineered lactose.

Materials and Methods

Lactose (Pharmatose 325M) was purchased from DMV (Netherlands). Micronised salbutamol sulphate was purchased from Allchem International, UK and was further micronised using an air jet microniser (JM-80, M & M Fryma Ltd., UK) with a nozzle pressure set to 6 bars. Polyvinylpyrrolidone (PVP) (Kollidon 90F, BASF, UK). Absolute ethanol was a standard reagent grade. Deionised water was produced with a reverse osmosis unit (Select analyst HP, Purite Ltd, UK). Aerolizer (Novartis Pharmaceuticals, UK) and gelatin capsules (size 3, British Enterprises Ltd, UK).

Preparation of spray dried lactose
Two lactose solutions containing 80g lactose and 1g PVP in 1000 ml deionised water were spray dried using a laboratory scale Buchi mini-spray drier (Buchi AG, Flawil, Switzerland). Spray drying conditions were: inlet temperature 178-180°C, outlet temperature 138-140°C, pump feed rate 3 ml/min, aspiration 100% and atomizing air flow rate 800 L/h. The product was collected only from the collecting vessel and the underside of the lid of the cyclone.

Engineering spray dried lactose

Due to the cohesive nature of spray dried powders, 1g of spray dried lactose was first dispersed in 20 ml cold ethanol to separate the particles. To disperse further the particles, the dispersion was aerosolized via a glass inhaler device into a glass flask of a filtration unit (Millipore, UK) containing 100 ml boiled ethanol. The turbulent air flow within the flask maintained the particles dispersed during the engineering process until hollow volume of the particles had grown to the desired size (Larhrib and Okpala, 2003). The engineered particles were recovered after 1min by filtration and deaggregated to generate single particles before were left to dry for 24 h in a ventilated oven (Model U, Memmert, Germany).

Bulk density measurements
The powder was transferred carefully into a pre-weighed 10 ml measuring cylinder and the bulk volume of the powder was determined. The bulk density was calculated as the ratio of the powder weight to the bulk volume of the powder.

Powder X-Ray Diffraction
Powder X-ray was performed on the commercial, spray dried and engineered products using an X-ray diffractometer (MiniFlex, Rigaku, UK). The analysis was carried out between 5 and 45 degrees, sampling every 0.01 degree with a scan speed of 5°/min

Characterisation of particle shape and size by Scanning electron microscopy.
Scanning electron micrographs of commercial, spray dried and engineered lactose were obtained using a scanning electron microscope (Jeol, JSM-U3).

Preparation of powder formulations
Salbutamol sulphate and lactose (Pharmatose or engineered) were mixed in a ratio of 1:67.5 w/w. 20 ml Stoppered vials, containing the separate blends of salbutamol sulphate with lactose, were placed in a Turbula® shaker mixer (Glen Mills, USA) and mixing was carried out for 30 min at 42 rev/min. All blends were filled into hard gelatin capsules (size 3) manually such that each capsule contained 27.4 $\pm$ 0.1 mg of powder.

HPLC analysis of salbutamol sulphate
Salbutamol sulphate was analysed by HPLC employing a mixture of methanol and 0.25% w/v 1-heptane sulfonic acid sodium salt water solution (40:60, v/v) as the mobile phase running at a flow rate of 0.9 ml/min and UV detection at 225 nm. The HPLC system consisted of a pump (HPLC PUMP 422, Kontron instruments, Italy), an autosampler (HPLC Autosampler 465, Kontron instruments, Italy), a multiple wavelength UV detector (UV/VS detector 785A, Perkin Elmer, USA) and a Symmetry® C18 column (150mm x 3.9mm I.D., Waters, USA). The injection volume was 20 μl. All the analysis was carried out at 21°C.

HPLC analysis of lactose
The HPLC system consisted of an autosampler (WPALS 1100 series, Agilent), a pump (isopump 1100 series, Agilent), a refractive index detector (RI 1200 series, Agilent technologies) and a APS-2 Hypersil column (100 mm x 3mm I.D., Thermo Electron corporation). The peak areas were analysed with a computer controlled software (ChemStation for LC, Rev. A. 10.02 [1757], Agilent Technologies). Mobile phase consisted of acetonitrile: water 70:30 v/v running at a flow rate of 1 ml/min; the injection volume was 10 μl. All the analysis was carried out at 21°C

Deposition test of powder formulations
Deposition of salbutamol sulphate and lactose from each powder blend was determined using a twin stage impinger after aerosolisation of 3 capsules at 60, 90 and 24 l/min via an Aerolizer.

Results and Discussion

Figure 1 shows the scanning electron micrographs of spray dried lactose-PVP before (Fig. 1a) and after engineering (Fig. 1b) respectively. Spray dried lactose-PVP particles are small (2-5 μm) with smooth surfaces. Contacting the particles with boiled ethanol increased their size and hollow volume without deviation from their spherical shape. The engineered particles have a rough surface (presence of hairs or projections), which stabilize the mix against vibration, thus avoiding percolation segregation. Furthermore, the surface roughness increases the specific surface area and hence the carrying capacity of the carrier particles.

It was not possible to measure the bulk density of spray dried lactose-PVP due to the cohesiveness and sticky nature of the material. The bulk density of the engineered spray-dried lactose-PVP was 3 fold smaller compared to commercial Pharmatose. The bulk densities were 0.18 $\pm$ 0.01 and 0.54 $\pm$ 0.03 gr/cm^3 respectively. The lower density of engineered lactose-PVP could be attributed to the presence of hairs and/or the increase in the particles hollow volum-ray powder diffraction results (Figure 2) showed that lactose-PVP has lost its crystallinity after spray drying as suggested by the presence of a flat X-ray pattern. Some crystallinity was recovered by the engineering process as

suggested by the presence of peaks in the diffractogram. The rate and extent of this recovery depends on the solvent temperature and on the duration of particles exposure to the solvent.

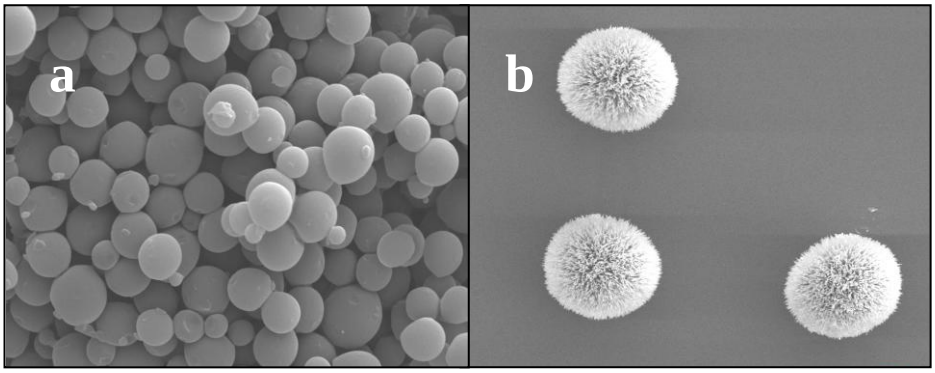

Figure 1: Scanning Electron micrographs of a) Spray dried lactose and b) Engineered lactose

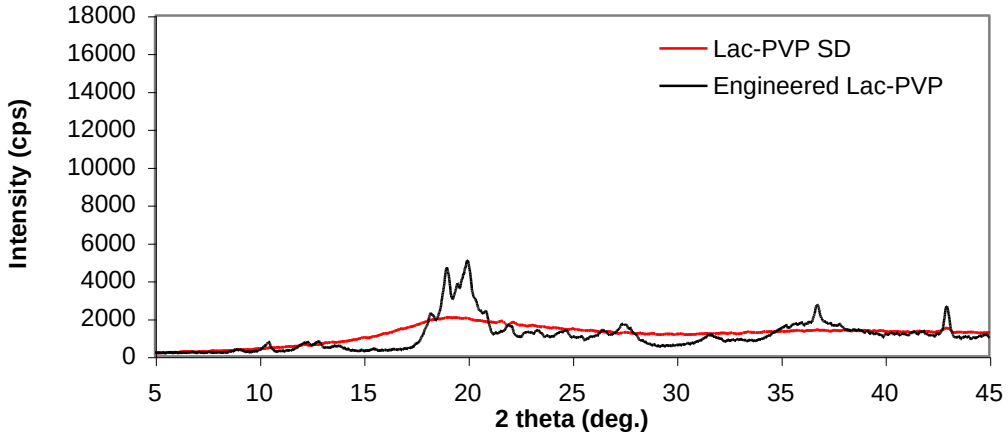

Figure 2: X-ray pattern for the spray dried and engineered lactose

Drug content uniformity

Formulations containing commercial or engineered lactose showed a percentage coefficient of variation (%CV) below 5%. This suggests that the overall process of mixing, sampling and analyzing was accurate and reproducible.

The deposition profiles of salbutamol sulphate and lactose at different flow rates

Powder formulations containing commercial lactose and engineered lactose as the carrier produced differences in the deposition of salbutamol sulphate (Table 1). The % recovery (%RD) was higher than 90% for all formulations and at different flow rates, suggesting that the washing procedure was accurate and reproducible. The Emitted dose (%ED) was strikingly high and up to 94% from the formulation containing engineered lactose suggesting good emptying of the drug from the capsule and device. Fine particle fraction (%FPF) and dispersibility (%) increased with flow rate for all the formulations. However, the formulations containing engineered lactose produced a higher FPF and dispersibility at any inhalation flow rate compared to commercial lactose irrespective of the size fraction used. The difference in FPF between formulations containing engineered and commercial lactose became more significant as the flow rate decreased.

The deposition profile of lactose is showed in Table 2. The recovered dose was similar for all formulations, however, a better emptying of the capsule and device was observed from commercial formulations. The presence of hairs on the carrier or the nature of the polymer may have contributed to the adhesion of lactose with the walls of the capsule or the device. The emptying of engineered lactose was flow rate dependent contrary to commercial lactose. Despite these results, once aerosolized, the dispersibility of engineered lactose becomes much more efficient as mirrored by large amount of lactose reaching the lower airways. The amount of engineered lactose was up-to 11 fold higher than commercial lactose. It was interesting to note that the amount of commercial lactose in the lower stage was independent on the flow rate, whereas the quantity of engineered lactose reaching the lower stage was flow rate

dependent and increased as the flow rate was reduced. The increase in efficiency of engineered lactose at low inhalation flow rate could explain the larger difference observed in drug FPF between formulations composed of commercial and engineered lactose.
At low inhalation flow rate (24 L/min), lactose deposition in the lower stage was higher than drug deposition, suggesting that deposition of the drug would have been improved if drug particles were strongly adhered to the carrier.

Table 1: Deposition results of Salbutamol Sulphate

Formulation	Flow rate (L/min)	ED (%)	FPF (%)	Dispersibility (%)
CL < 63μm	90	84.6 ± 1.7	30.7 ± 1.8	36.2 ± 1.3
	60	86.1 ± 1.4	21.0 ± 1.7	24.4 ± 1.7
	24	85.6 ± 0.6	9.1 ± 0.6	10.7 ± 0.8
CL 63-106μm	90	83.8 ± 3.3	24.7 ± 1.0	29.5 ± 0.0
	60	80.0 ± 2.3	17.6 ± 0.9	22.0 ± 1.3
	24	84.2 ± 1.2	7.1 ± 0.8	8.4 ± 1.1
Engineered Lac-PVP <63μm	90	94.6 ± 0.6	50.4 ± 1.7	53.3 ± 1.5
	60	93.1 ± 0.8	40.0 ± 1.4	43.0 ± 1.2
	24	89.8 ± 0.5	21.6 ± 0.9	24.0 ± 0.9

Table 2: Deposition results of Lactose

Formulation	Flow rate (L/min)	CAP+INHALER (%)	US (%)	LS (%)
CL 0-63μm	90	4.5 ± 0.5	91.2 ± 1.2	4.4 ± 0.7
	60	6.1 ± 0.8	89.1 ± 1.2	4.9 ± 0.6
	24	7.1 ± 1.2	89.1 ± 1.5	3.9 ± 0.4
CL 63-106μm	90	4.5 ± 1.0	90.9 ± 0.5	4.4 ± 0.4
	60	4.2 ± 0.7	91.7 ± 1.2	4.1 ± 0.6
	24	4.1 ± 0.7	91.7 ± 1.9	4.2 ± 1.2
Engineered Lac-PVP <63μm	90	5.1 ± 0.7	70.1 ± 1.4	24.8 ± 0.7
	60	9.3 ± 1.2	62.1 ± 1.7	28.6 ± 0.7
	24	17.9 ± 2.0	47.0 ± 1.9	35.2 ± 0.1

Conclusion

This study has shown a novel engineering process capable of producing an elegant carrier for dry powder inhalation, with many desired properties such as, good flow properties, high uniformity in size and shape, high drug loading capacity, low density and crystallinity.
The engineered carrier has improved salbutamol sulphate deposition at any flow rate compared with Pharmatose commercial carrier. The engineered carrier performs better at low inhalation flow rate as shown from lactose deposition data. Therefore, it could be suitable for patients who can not generate a high inhalation flow rate. The carrier has a longer time of flight, thus it has the potential to deliver sticky drugs. The most important aspect of this work is that the adhesion of drug to the carrier could be beneficial in improving the drug deposition profile. Adhesion of drug to the carrier has always been seen as a negative effect on the aerosol performance, however, it could also be advantageous as shown from the present work.

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