Enhancement of Small Particle Size Dry Powder Aerosol Formulations using an Ultra Low Density Additive

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INTRODUCTION

The principal requirement for the development of an effective and efficient dry powder system for pulmonary drug delivery is that the mass median aerodynamic diameters of particles comprising the generated aerosol cloud should be in the range 1.0–5.0 μm (1). More critically, where the pulmonary route is being considered for systemic drug administration and targeting to deep lung regions is required, the particle diameter window is reduced to 1.0–2.0 μm (2). While particles of these diameters are respirable, the magnitude of their high inherent surface electric forces produce cohesive powder systems (3). For this reason, formulation must improve the poor flow properties of such powders if device filling and subsequent emptying are to be efficient and reproducible.

The performance of many current DPI formulations relies on the formation of ordered units between fine drug crystals and coarse carrier particles. However, the efficiency of separation of these two particle types on inhalation is often poor and suggests dominance of adhesive forces within the ordered units. One strategy shown to increase redispersion of drug into the respirable aerosol is the use of a smaller particle size carrier (5) although the poor flow behaviour of these formulations can be problematic in device emptying. Where this is the case, a potential solution is the enhancement of flow properties through reducing bulk densities (6); the loose packing of particles promoting an open powder structure which will flow more readily (7). Such effects could be produced by the generation of high porosity particles (8) or by inclusion of an excipient which modifies the bulk properties of the formulation. In the present study, we have pursued this latter strategy through production of a low density form of L-leucine by spray-drying. The potential of this material to facilitate emptying of formulations of a model small molecule drug from a multi-dose pre-metered inhaler device has been examined.

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ABBREVIATIONS: DPI, dry powder inhaler; ECD, effective cut-off diameter; FPL, fine particle lactose; VMD, volume mean diameter.

MATERIALS AND METHODS

Materials

Salbutamol sulphate was obtained as a micronised powder from Leiras Oy (Turku, Finland). Fine particle lactose was used as received (Sorbolac 400; Meggle, Wasserburg, Germany). Coarse carrier lactose (63–90 μm fraction) was prepared from α-lactose monohydrate (D30; Meggle) by two-stage sieve classification. The naturally occurring amino acid L-leucine was obtained from Ajinomoto Co. (Tokyo, Japan); this excipient is generally regarded as safe. Water used was MilliQ grade (Millipore, Watford, U.K.). Empty 4-place disk blisters for the Diskhaler® device were a gift from Glaxo Wellcome.

Preparation of Spray-Formed L-Leucine

L-leucine was prepared using a laboratory scale co-current spray-dryer (Model 191, Büchi, Switzerland). Solutions of L-leucine in water (1% w/w) were atomised at a constant rate of 4.5 ml min^{-1} using compressed air (600 l hr^{-1}, 0.7 mm nozzle). Inlet and outlet temperatures were 220°C and 150°C respectively. Following spray-drying the product powder was transferred to a glass container and stored over silica gel until used.

Chemical Identification

Chemical identity of bulk L-leucine and spray-processed material was determined by infra-red spectroscopy and measurement of specific optical rotation. For infra-red analysis, potassium bromide disks of each material were prepared and scanned between 400–3500 cm^{-1} (Model 782 infra-red spectrophotometer, Perkin Elmer, Buckinghamshire, U.K.). Optical activity of L-leucine and the spray product was determined in 6M HCl using the D line of sodium. Rotation was measured in 2 dm tubes using an automatic photoelectric polarimeter (Optical Activity Ltd., Huntingdon, U.K.) and data expressed as the specific rotation at 20°C ($[\alpha]_o^{20}$.

Powder Characterisation

Particle size distributions of powders were determined by laser diffraction (MasterSizer X, Malvern Instruments, Malvern, U.K.). Size analysis was carried out in liquid suspension using cyclohexane + 0.1% w/w lecithin (BDH Ltd, Poole, U.K.) presaturated with appropriate excipient. The size distributions were expressed in terms of the volume mean diameter (VMD) and the diameters below which 10% and 90% by volume of the particles in the powder resided. Particle morphology was imaged by scanning electron microscopy (JSM 6310 SEM, JEOL, Tokyo, Japan) under low temperature conditions (CT1500 Cryotrans Unit, Oxford Instruments, Oxford, U.K.). Poured and tapped densities of powders were measured using a jolting volumeter (Engelsmann, Germany) and Carr's compressibility index calculated as a measure of flow (6).

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Table I. Bulk Properties of Powder Excipients

Compound	Poured density (g cm^{-3})	Tapped density (g cm^{-3})	Carr's Index (%)	VMD (μm)	<90% (μm)	10%< (μm)	$[\alpha]_D^{20}$
L-leucine (Bulk Powder)	0.71	0.77	8.5	372.7	518.4	244.0	15.4
L-leucine (Spray-Dried)	0.03	0.04	28.6	6.7	14.1	0.8	15.4
Lactose (63–90 μm)	0.75	0.82	8.6	98.1	156.8	8.4	N.D.[a]
FPL	0.32	0.56	42.9	7.2	16.1	1.1	N.D.[a]

Note: $[\alpha]_D^{20}$ Specific optical rotation at 20°C.
[a] N.D. Not determined.

Preparation of Powder Aerosol Formulations

Salbutamol sulphate was formulated using either coarse carrier lactose or fine particle lactose. For coarse-carrier formulations, salbutamol sulphate (VMD = 2.2 μm) was mixed at concentrations of 240 μg/125 mg and 240 μg/7.5 mg with α-lactose monohydrate (63–90 μm) using a turbulent tumble mixer (90 rpm, 30 min; Turbula T2C, Bachofen, Switzerland) with coarse sieving after 10 mins (150 μm aperture sieve). Salbutamol sulphate content of these formulations is within the therapeutic range used in commercially available DPIs. Where fine particle lactose rather than coarse lactose was to be used as the carrier in formulations, salbutamol sulphate and FPL were first mixed in a glass mortar using a metal stirrer for 30 minutes. This pre-mix containing salbutamol sulphate at a concentration of 240 μg/7.5 mg was subsequently transferred to high density polyethylene containers (135 ml) and hand-blended (10 min) with spray-dried L-leucine to final concentrations of 5.0, 10.0 and 15.0% w/w. The degree of homogeneity was expressed by the coefficient of variation (CV) of sample drug content (n = 10); blended powders with CV's < 5% were considered to be satisfactorily mixed. Quantitative analysis of salbutamol sulphate was by fluorimetry (λ_{ex} = 275 nm, λ_{em} = 305 nm). Fine particle blends (7.5 mg) and coarse-carrier formulations (7.5 and 25 mg) were filled into 4-place disk blisters which were heat sealed before use.

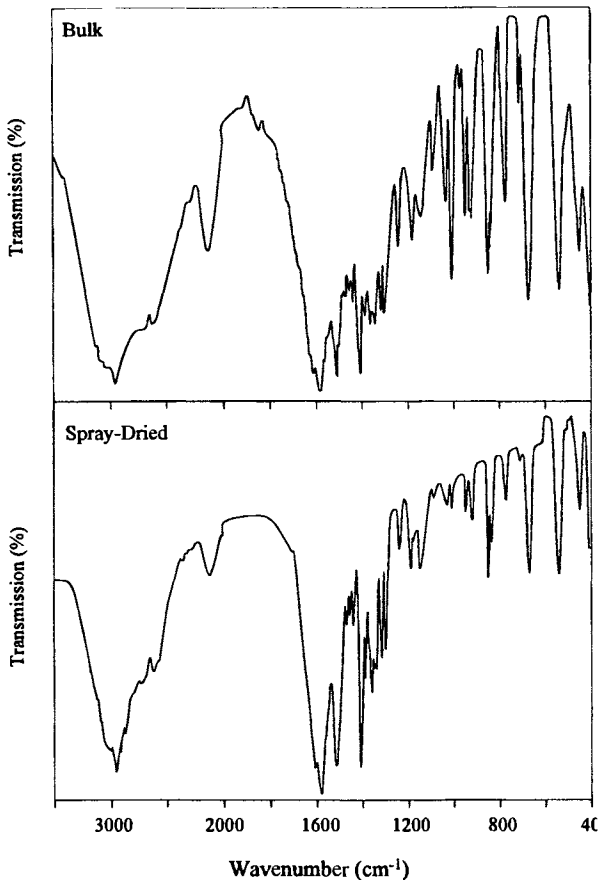

Fig. 1. Infra-red spectra (KBr disks) of bulk crystalline L-leucine powder and the spray-dried L-leucine powder.

In Vitro Aerosol Performance

The aerosol performance of powder formulations was determined using a modified version of Apparatus A (BP 1993, Appendix XVIIC), a glass twin stage impinger calibrated at 60 ± 5 l min^{-1}. For these studies the 14 mm internal diameter of the standard stage 1 jet (9) was reduced to 11.4 mm in order to change the calculated effective aerodynamic 50% cut-off diameter (ECD_{50}) from 6.4 μm to 4.9 μm. A separate independent calibration was carried out and determined the ECD_{50} to be 5.3 μm (AEA Technology, Havant, Hampshire). The aerosol performance parameters measured were the percent of the loaded dose retained in the device, fine particle fraction (FPF) and dispersing efficiency. The last two measures are defined as the percent of drug emitted from the device reaching stage 2 of the impinger and the mass of drug in stage 2 of the impinger as a percentage of the dose loaded in the device.

Statistical analysis of data was carried out using Minitab statistical software (Addison-Wesley Inc., MA). Post-ANOVA analysis was carried out by Fishers method.

RESULTS AND DISCUSSION

Physical Characterisation of L-Leucine Following Spray-Drying

In the bulk form L-leucine was obtained as a free-flowing coarse crystalline solid. However, processing of this material by spray-drying from a 1% w/w solution yielded a powder with a substantially different physical appearance. Most noticeably, the loose white powder product generated an aero-colloid on agitation. As shown in Table I the processing of L-leucine by spray-drying was also associated with a reduction in the particle

size from 372.7 μm (VMD) for the bulk material to a measured diameter of 6.7 μm for the spray-dried powder. This effect is similar to that which can be achieved through processing the material by fluid-energy jet milling. However, where jet-milling would typically have been expected to reduce the poured density of the material from 0.71 g cm^{-3} to between 0.30 and 0.45 g cm^{-3} spray-drying of L-leucine from solution generated a product having a poured density of 0.03 g cm^{-3} (Table I). Confirmation that this low density material was a different physical form of L-leucine rather than a decomposition product produced during spray-drying was made by comparison of infra-red and optical behaviour; Infrared spectra for both the spray-dried

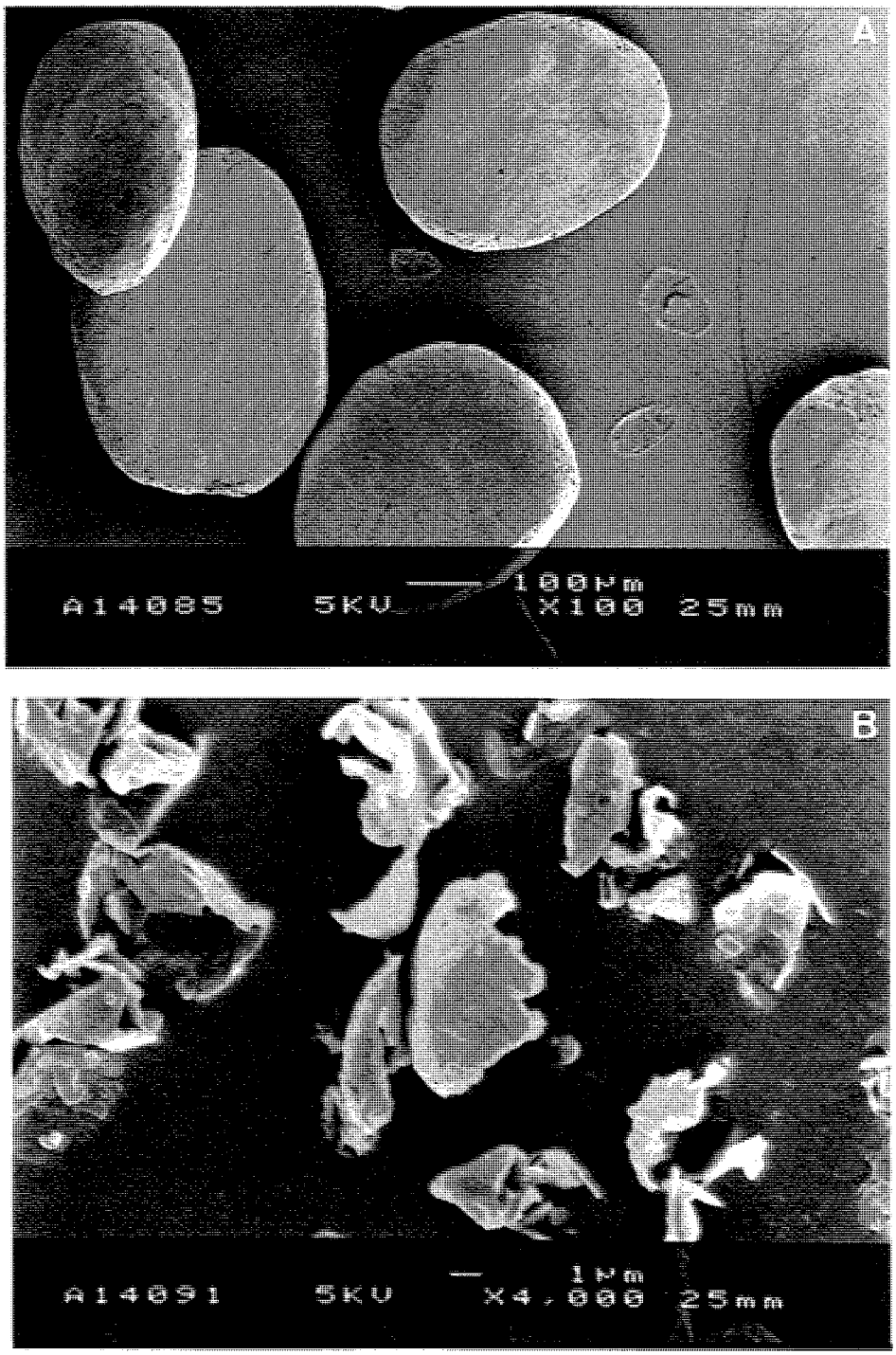

Fig. 2. Scanning electron micrographs (at different magnifications) of L-leucine powders (A) bulk crystalline L-leucine powder used to prepare the spray-drying feed solution and (B) the spray-dried L-leucine powder.

product and bulk materials were found to be identical (Fig. 1) and the measured value of specific optical rotation was +15.4° for both materials (Table I). Therefore, spray drying appeared only to change leucine particle morphology with no chemical changes being induced.

For example, particles of the bulk material (Fig. 2a) existed as oblate spheroids, whereas the spray-dried powder appeared to be composed of fractured hollow spheres (Fig. 2b). These particles were found to be constituted of curved plates of nanometer thickness which are capable of space filling thereby producing open rather than packed powder structures. Production of particles with this morphology was considered simply to reflect the energetics of the drying process and the material properties of this system; fracturing being produced in conditions where the temperature of the drying gas is greater than the solution boiling point and the drying-droplet crust is rigid and of low porosity (10).

Aerosol Performance of Salbutamol Sulphate Formulations

Particle Size Effects on Formulation Performance

In formulating salbutamol sulphate as a dry powder for delivery from the Diskhaler®, α-lactose monohydrate was included as a carrier and diluent. For binary systems prepared using coarse lactose (63–90 μm fraction) a high degree of homogeneity was exhibited following mixing. The co-efficient of variation of sample drug content for both blends being <1.5%. In the case of formulations based on fine particle lactose (FPL), acceptable homogeneity of drug distribution (CV = 2.9 %) was found after 30 minutes mixing.

For these formulations, carrier-particle diameter was found to have a significant influence on aerosol behaviour (Table II). Analysis of variance on fine particle fraction data indicated that redispersion of salbutamol sulphate was significantly higher from FPL than coarse carrier lactose (ANOVA; $p < 0.05$). This was considered to occur as the low surface roughness of fine particles reduces the magnitude of adhesive contacts (11). In accordance with the earlier observations of Ganderton (12) the drug detachment from carrier particles was also found to be increased with modification of the salbutamol sulphate concentration from 0.96% w/w (240 μg/25mg) to 3.2% w/w (240 μg/7.5 mg). However, the reduction in dose weight from 25 to 7.5 mg necessary to maintain the nominal salbutamol sulphate dose at 240 μg was a constraining factor in adopting this strategy as the proportion of the drug retained in the device increased from 12.5 ± 1.6% to 34.9 ± 2.6%; at the low fill weight disproportionate powder retention on the actuator pin of the Diskhaler® was evident.

Evaluation of Spray Dried L-Leucine as a Flow-Agent in Dry Powder Aerosol Formulations

Given the experimental evidence reported in the previous section, the use of small particle size carriers appears to offer an opportunity to increase redispersion of salbutamol sulphate as a discrete component of the aerosol cloud. However, overall formulation performance is also determined by the extent of drug retention in the inhalation device. For FPL systems this is significant with 20.2 ± 1.2% of the loaded drug dose retained in the device compared with 12.6 ± 1.6 % (Table II) for a coarse lactose system (25 mg fill weight). Given the physical properties of spray-dried L-leucine it was considered that addition of such an ultra-low density component to formulations of salbutamol sulphate and FPL might improve their flow behaviour. Indeed, where this hypothesis was tested through modification of a powder blend of salbutamol sulphate and FPL by inclusion of 15% w/w spray-dried L-leucine the retention of drug in the device was reduced to a level comparable to the low-dose coarse carrier system. Improved device emptying was also evident with a formulation containing 10% w/w L-leucine (ANOVA; $p < 0.05$). Importantly, however, the inclusion of this excipient has no significant negative effect on formulation homogeneity; co-efficient of variations for salbutamol sulphate content of blends containing 0%, 5%, 10% and 15% L-leucine were 2.9%, 4.9%, 2.8% and 3.4% respectively.

That such additions of L-leucine significantly improved device emptying is a probable reflection of the changes in the bulk properties of the powders. Mechanistically, the increase in bulk volume would be expected to generate flow-improvements as interactions between particles is reduced in less tightly packed systems; a lower driving force being required to overcome frictional drag and initiate powder flow. However, it is also considered that some of the functionality of L-leucine in improving powder flow may result from the previously demonstrated anti-adherent action of this material (13).

In terms of redispersion of salbutamol sulphate from the FPL formulation the addition of L-leucine was found to have no significant effect on the fine particle fractions of this drug.

Table II. Influence of Spray-Dried L-leucine on the In Vitro Salbutamol Sulphate Deposition from the Diskhaler®

Formulation	Poured density (g cm^{-3})	Tapped density (g cm^{-3})	Carr's index (%)	Device retention (%)[a]	Fine particle fraction (%)[b]	Dispersion efficiency (%)[a]
Salbutamol Sulphate-coarse lactose (240 μg/25 mg)	0.71	0.78	9.2	12.5 (1.6)	11.1 (1.6)	9.3 (1.5)
Salbutamol Sulphate-coarse lactose (240 μg/7.5 mg)	0.70	0.80	12.5	34.9 (2.6)	16.5 (1.4)	10.2 (1.1)
Salbutamol Sulphate-FPL	0.32	0.55	40.7	20.4 (1.2)	24.5 (1.9)	18.6 (1.7)
Salbutamol Sulphate-FPL + 5% w/w L-leucine	0.25	0.40	37.1	17.7 (2.2)	27.4 (3.6)	23.0 (2.4)
Salbutamol Sulphate-FPL + 10% w/w L-leucine	0.22	0.32	31.3	13.2 (1.7)	25.8 (3.8)	21.9 (2.5)
Salbutamol Sulphate-FPL + 15% w/w L-leucine	0.18	0.25	28.4	11.1 (0.9)	23.9 (2.6)	21.1 (1.8)

Note: Air flow rate 60 l min^{-1}. Values are mean ± SD (n = 5).
[a] Results are percent of loaded dose.
[b] Results are percent of emitted dose.

Consequently overall device performance, as indicated by the dispersion efficiency, was maintained at a level significantly above that of coarse carrier systems.

In conclusion, this study demonstrates the use of a spray-drying technique to produce a unique physical form of the amino acid L-leucine which exhibited utility as a flow aid. The inclusion of this ultra low density excipient was found to improve the discharge of a salbutamol-fine particle lactose blend from the Diskhaler® device.

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