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In vitro characterisation of terbutaline sulphate particles prepared by thermal ink-jet spray freeze drying

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ABSTRACT

Thermal ink-jet spray freeze-drying (TIJ-SFD) was used to produce inhalable particles of terbutaline sulphate, the aerosolisation properties of which were compared to the commercial Bricanyl® formulation. Scanning electron micrograph images showed the particles to be spherical, highly porous and suitable for aerosolisation from a simple, capsule-based dry-powder device (Cyclohaler®) without the need for additional excipients. Particle size was dependent upon the concentration of solution jetted, as well as the distance between the print head and the surface of the liquid nitrogen. Starting with a 5% (w/v) solution and maintaining this distance at 3 cm produced spherical, porous particles of volume median diameter (VMD) 14.1 ± 0.8 μm and mass median aerodynamic diameter (MMAD) 4.0 ± 0.6 μm. The fine particle fraction (proportion of aerosol with MMAD ≤ 4.46 μm) was 22.9 ± 3.3%, which compared favourably with that of the marketed dry powder inhaler formulation of terbutaline (Bricanyl® Turbohaler®; 25.7 ± 3.8%), tested under the same conditions. These findings show that TIJ-SFD is a useful tool to predict the viability of a DPI formulation during preformulation physicochemical characterisation.

1. Introduction

Dry powder inhaler (DPI) formulations are attractive in terms of patient compliance, they are breath-actuated, do not require propellants and involve the preparation of relatively simple powder blends. Particle size is critical to successful DPI formulation, the drug needing an aerodynamic diameter less than approximately 6 μm to penetrate the deep lung, and even smaller if the alveolar region is the therapeutic target (Pritchard, 2001). Powders in this size range are usually difficult to aerosolise because of their inherent cohesiveness (Timsina et al., 1994). Consequently, in typical DPI formulations small drug particles are bound by a force of adhesion to the surface of a larger, crystalline carrier (often lactose) to improve powder flow and aerosolisation properties (Prime et al., 1997). Alternatively, the drug particles can be allowed to form loose agglomerates, which achieves the same improvement in powder flow but without additional excipients. The aerosol performance of a DPI formulation, usually characterised by mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF), is critically dependent upon the complex interplay between particles in the powder blend. These interactions involve the force of cohesion in the case of an agglomerated powder formulation, or the force of adhesion where a coarse carrier, such as lactose, is employed. In either case, the force of adhesion/cohesion must be sufficiently high to produce a powder with good flow properties (to allow accurate filling of doses and liberation of powders from delivery devices), but not so high that disaggregation cannot be achieved in the turbulent air stream created by patient inspiration, to generate a fine particulate drug aerosol, capable of deep lung penetration.

Formulation and in vitro testing of DPI formulations usually requires considerable amounts of material, where the active is prepared by micronisation or spray-drying, and so the pulmonary route might not be evaluated early during preformulation when little drug substance may be available. We showed in a previous paper (Mueannoom et al., 2012) how thermal ink-jetting (TIJ) into liquid nitrogen can produce frozen particles which may subsequently be lyophilised (spray freeze drying, SFD) to produce particles in the micrometre size range. The small volumes of liquid that could be jetted (0.2–0.5 mL) opened the possibility of assessing the viability of pulmonary formulations with greatly reduced amounts of material than is usually the case. An additional benefit of the technique is that the particles produced were excipient-free. We showed how excipient-free salbutamol sulphate particles (usually formulated with coarse carrier particles of lactose in marketed DPI products) could be engineered by TIJ-SFD, and compared their aerodynamic performance to a commercial formulation.

Some inhalable drugs, however, can be formulated as "soft aggregates" by spheronisation, capable of generating an aerosol of inhalable size, without the inclusion of additional excipients (Wetterlin, 1988). Consequently, the Turbohaler®/Turbuhaler®

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device (Braunstein, 1992) has been developed to deliver, excipient-free aggregates of budesonide (Pulmicort®) and terbutaline sulphate (Bricanyl®). The specific aim of this research, therefore, is to measure the aerosolisation properties of terbutaline sulphate particles produced with TIJ-SFD, which are excipient-free, and to determine whether such particles are equivalent to those of a commercial agglomerated-powder formulation. If so, preparation of particles with TIJ-SFD during preformulation characterisation would be an indicator of their likely behaviour in a commercial device.

2. Materials and methods

Terbutaline sulphate (TBS) was purchased from Sigma–Aldrich Ltd. (UK). Silicone oil (density 1.05 g cm^{-3}) and 1-hexanesulphonic acid sodium salt hydrate (99%+) were purchased from Acros Organics (USA). Methanol and glacial acetic acid (both HPLC grade) were purchased from Fisher Scientific (UK). All materials were used as received. Aqueous solutions were prepared using deionised water. Cyclohalers® and Bricanyl® Turbohalers were purchased from AAH Pharmaceuticals (UK).

2.1. Thermal ink-jet spray-freeze drying

A modified Hewlett-Packard Deskjet 340 printer (Mueannoom et al., 2012) was used throughout. Aqueous TBS solutions (5 and 10% (w/v)) were loaded into the printer cartridge and jetted into liquid nitrogen. The distance between the print head and the surface of the liquid nitrogen was maintained at either 3 or 4 cm. Typically, 45 cycles were printed before the excess liquid nitrogen was allowed to evaporate and the sample was transferred to a freezer (−20 °C). Freeze-drying was accomplished with a Modulyo D-230 (Thermo Scientific, UK). The sample shelf was equilibrated at −50 °C before the sample was loaded and then placed under vacuum (0.5 mbar). The sample was held under these conditions for 22 h before commencement of a secondary drying stage at 10 °C for a further 6 h. Samples were stored in a vacuum desiccator over phosphorous pentoxide.

2.2. Particle sizing

Particle size distributions ($n = 10$) were measured with a HELOS/BR laser diffractometer (Sympatec GmbH, Germany). Two sample dispersion techniques were used. For RODOS (dry powder) measurements, samples were placed in the powder feeder and pressurised air (4 bar) was used to disperse the powder into the measurement chamber. For INHALER (DPI device) measurements samples (10 mg) were weighed into hard gelatin capsules (size 3), loaded into a Cyclohaler® device and dispersed into a low pressure (4 mbar) air stream. An R4 lens (0.5–350 μm) was used to collect data. Data were analysed with the Windox 5 software.

The size distribution of droplets produced by the printer cartridge was analysed using a Malvern 2600c laser diffraction size analyser with 63 mm lens (Malvern Instruments Ltd., UK). The jet nozzle was clamped 2.5 cm from the centre of the laser beam and adjusted to permit the spray generated to traverse the beam at a distance of 2.5 cm from the lens of the instrument. A vacuum was applied to draw the aerosol through the beam.

2.3. Electron microscopy

Samples were mounted on double-sided adhesive tape, placed on aluminium stubs and sputter-coated (3 min at 40 mA) with gold to a thickness of 10 nm (Quorum model Q150) before being imaged. Images were collected using a scanning electron microscope (SEM, Quanta 200 FEG, FEI, Netherlands).

2.4. X-ray powder diffraction

X-ray powder diffraction (XRPD) data were recorded with a PW3830 (Philips, Netherlands) using a Cu Kα X-ray source operated at 40 mA, 40 kV with an angular increment of 0.05° s^{-1}. Measurements were taken from 0 to 30° on the 2θ scale.

2.5. Thermal analysis

Modulated temperature differential scanning calorimetry (MTDSC, Q2000, TA Instruments LLC, USA) was used over the temperature range; room temperature to 280 °C, with an underlying heating rate of 2 °C min^{-1}. The modulation parameters were amplitude 1 °C, period 60 s. Samples (4–6 mg) were loaded into aluminium T-zero pans fitted with non-hermetic aluminium lids. The cell constant and enthalpy calibrations were performed with indium (Certified Reference Material LGC2601, Batch E1, LGC, London, $T_m = 156.61$ °C, $\Delta H_f = 28.70$ J/g) in accordance with the manufacturer's instructions. The measured values were always in excellent agreement with those of the reference material (T_m ±0.03 °C, ΔH_f ±0.1 J/g). Nitrogen (50 mL min^{-1}) was used as a purge gas and data were analysed with Universal Analysis 2000.

Thermogravimetric analysis (TGA, Pyris 6, Perkin-Elmer Ltd.) was used from room temperature to 280 °C at 10 °C min^{-1}. Samples (4–6 mg) were weighed into a ceramic crucible. Nitrogen (20 mL min^{-1}) was used as a purge gas. The mass loss between 40 and 100 °C was used to determine water content of samples.

Dynamic vapour sorption (DVS-1, SMS Ltd., UK) was operated at 25 °C. Samples (2–3 mg) were loaded into the pan and allowed to equilibrate under a dry atmosphere for 10 h. The RH was then increased in discrete steps (5% h^{-1}) to 90%.

2.6. HPLC analysis of terbutaline sulphate

A calibration curve for TBS was prepared using High Pressure Liquid Chromatography (HPLC) fitted with a UV-detector (Hewlett Packard, Germany) using a mixture of 5 mM sodium-1-hexanesulphonate in water and methanol (75:25%, v/v) containing glacial acetic acid (1%, v/v) as the mobile phase, delivered at a rate of 1.0 mL min^{-1}. The stationary phase was a Luna Phenomenex C18 column (250 mm × 4.6 mm) kept at 40 °C. The injected sample volume was 10 μL. Peaks were measured at 276 nm and the method produced a linear response ($r^2 = 0.9998$) for terbutaline sulphate concentrations of 1.0 and 100 μg/mL. The retention time of samples on the column was 7.5 min.

2.7. Aerosol performance

Deposition profiles were determined with apparatus E (next generation impactor, NGI, Copley Instruments Ltd., UK) operated under standard conditions (Appendix XII part C, British Pharmacopoeia 2010).

The Cyclohaler® (SFD particles) or Turbohaler (Bricanyl® commercial TBS formulation) was attached to the NGI via a rubber mouthpiece adaptor and tested at 60 L min^{-1} for 4 s. Prior to use, the impaction cups in each of the 7 stages were coated with 1% (w/v) silicone oil in hexane and allowed to dry for 30 min. The surface coating prevented 'bounce' and re-entrainment of particles between stages. Ten capsules (size 3), manually filled (5–7 mg SFD powder in each) were discharged from the Cyclohaler, or ten doses (500 μg/actuation) were delivered from the Turbohaler into the NGI. After actuation the contents of the device, capsule, throat, pre-separator and each stage were washed with deionised water